AIR FORCE HEALTH STUDY

An Epidemiologic Investigation of
Health Effects in Air Force Personnel
Following Exposure to Herbicides

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IMMUNOLOGIC ASSESSMENT

INTRODUCTION

Background

Of the many chemical compounds known to cause immune system dysfunction in laboratory animals, the polyhalogenated aromatic hydrocarbons have been the most extensively studied and, among these, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, or dioxin) has proven to be the most toxic. Since the early 1970s, when TCDD was shown to cause marked involution of the thymus gland in numerous experimental animals (1-4), an extensive body of literature pertinent to TCDD-induced immunotoxicity has been summarized in the recent comprehensive review article by Holsapple and colleagues (5). In laboratory animals, TCDD has proven to have a wide range of toxic effects on all components of the immune system including the following:

- Compromised cell mediated (6,7) and humoral (8-10) immune function
- Impaired myelo-(11,12) and lymphoproliferative (11,13-15) responses
- Suppressed complement activity (16,17)
- Compromised host resistance to bacterial (8,11,17-19), parasitic (20), and viral (19,21) infections.

In an attempt to provide data more relevant to humans, two laboratories have conducted experiments into the effects of TCDD on numerous immunologic indices in marmoset (22-24) and rhesus monkeys (25). These studies, carried out in vitro in lymphocyte cell cultures and in vivo with single dose injections of TCDD in various concentrations, have yielded inconsistent results that in many cases do not fit a typical dose-response pattern. The relevance of these acute phase studies to the long-term occupational exposure more typical in humans remains to be proven. In none of the in vivo studies have the animals shown evidence of overt illness.

Much of the past and current basic research in laboratory animals has focused on the importance of the aryl hydrocarbon (Ah) receptor in some but not all manifestations of TCDD toxicity including suppressed humoral (10,26-32) and cellular (33,34) responses and impaired complement activity (35). Numerous additional studies have demonstrated that TCDD effects can occur independent of the presence of the Ah receptor (27,28,30-32,36-39). Although the Ah receptor has been defined in several human tissues (see references 40-45 in Chapter 9, General Health) the relevance of these observations to TCDD toxicity in humans remains controversial. Two comprehensive reviews have summarized the voluminous literature related to the mechanisms of TCDD immunotoxicity and the role of the Ah receptor (40,41). In contrast to the active research in animals, relatively few studies have been published describing immune system effects of TCDD in humans and from these studies

no consistent evidence for immunotoxicity has been found. Most reports have been based on populations exposed to TCDD as a consequence of industrial accidents, environmental contamination, or military service in Vietnam.

In early reports on a population at risk from soil contamination in Times Beach, Missouri, abnormalities in several indices of immune function were documented including impaired delayed hypersensitivity by skin testing and nonsignificant variations in several peripheral lymphocyte subsets and ratios (42,43). However, followup examinations of the same subjects found no differences between those exposed and the controls (44,45).

Reports of examinations conducted on individuals exposed in industrial explosions in England (46) and Seveso, Italy (47) noted minor variations in several immunologic indices, but none were of apparent clinical significance.

Finally, in the most recent report of the Air Force Health Study (AFHS) (48), in which immunologic indices were examined in relation to the current body burden of dioxin, a statistically significant increase in the IgA globulin fraction was noted in the Ranch Hand cohort. Although of uncertain significance, this finding is of interest given a report of a laboratory animal study (49) that documented a selective increase in the IgA fraction upon exposure to a single injection of TCDD. There were no other significant differences between the Ranch Hand and Comparison cohorts.

Summary of Previous Analyses of the Air Force Health Study

1982 Baseline Study Summary Results

Immunologic function and phenotypic marker studies were performed on 592 participants (297 Ranch Hands, 295 Comparisons) randomly selected by the terminal digit of their case number. Because of laboratory problems (e.g., fluctuating quality control and lack of simultaneous differential counts on the peripheral mononuclear cells), data could be analyzed on a group basis only.

Analyses of the cell surface markers (CD2 or T_{11}, CD3 or T_3, CD4 or T_4, CD8 or T_8, CD20 or B, the CD4-CD8 or T_4-T_8 ratio, and the total lymphocyte count (TLC) showed no significant group differences. However, increased smoking was significantly associated with increases in most cell counts but not with the CD4-CD8 ratio and CD20 cells, whereas increasing age was significantly associated with decreasing TLC and CD8 cells.

Functional studies of T and B cells via reaction to antigenic (tetanus toxoid) or mitogen (phytohemagglutinin [PHA], concanavalin A, and pokeweed) stimulation showed no group differences. Similarly, unadjusted and adjusted mean values of the four assays were not significantly different between groups.

In summary, neither immunologic function nor cell marker studies showed significant impairment in the Ranch Hand group, nor did they show patterns supportive of a herbicide effect. Smoking was associated with a significant increase in the marker cells CD2, CD3,

CD4, and CD8, and in the TLC, with a concomitant increase in lymphocytic response to pokeweed mitogen (PWM).

1985 Followup Study Summary Results

The 1985 AFHS physical examination placed more emphasis on the immunologic assessment than did the 1982 Baseline profile. Immunologic competence was measured by cell surface marker (phenotypic) studies and cell stimulation studies on 47 percent of the study population, and by a series of four skin test antigens in 76 percent of the participants to assess the delayed hypersensitivity response.

Surface marker studies were conducted for CD2 cells, CD4 cells, CD8 cells, CD20 or B cells, CD14 cells or monocytes, and HLA-DR cells; the ratio of CD4 to CD8 cells also was included in the analysis. Because of inherent significant day-to-day and batch-to-batch variation, all results (including functional stimulation studies) were adjusted for blood-draw day. Statistical testing of the seven phenotypic cell markers did not reveal any significant group differences, either unadjusted or adjusted, for the covariates of age, race, occupation, current smoking, lifetime smoking history (in pack-years), current alcohol use, or lifetime alcohol use (in drink-years). Similarly, none of the unadjusted or adjusted analyses of the functional stimulation studies (for PHA, PWM, or mixed lymphocyte culture [MLC]) showed any statistically significant group differences. Overall, no pattern was identified to suggest a detriment in any subgroup of either the Ranch Hands or Comparisons.

The effects of age, race, smoking, and alcohol use affected most variables in the phenotypic and stimulation studies. Consistently decreasing values of all cell markers and stimulated cells were associated with increasing age, whereas increased levels of smoking were usually associated with increases in the values of those variables. Blacks had consistently higher stimulated cell counts than non-Blacks, but this effect was not observed for counts of T cells, B cells, or HLA-DR cells. Enlisted personnel generally had higher cell surface marker counts than officers.

The delayed hypersensitivity response was assessed by the skin test antigens of mumps, *Candida albicans*, Trichophyton, and staph-phage lysate. The 48-hour measurements of skin induration and erythema for the four tests showed marked inter-reader variation. Consequently, all skin test data were declared invalid and were not used in the assessment of group differences. The skin test reading problems led to the use of additional clinical quality control procedures for the 1987 followup examination.

In conclusion, no significant group differences were found for the comprehensive cell surface marker or functional stimulation studies. The effects of age, smoking, and alcohol use were observed in these immunologic tests.

1987 Followup Study Summary Results

For the assessment of the 1987 immunologic examination data, composite skin reaction test results and various laboratory examination measurements from cell surface marker studies, three groups of functional stimulation tests, and quantitative immunoglobulins were

analyzed. Ranch Hands had a higher frequency of individuals with possibly abnormal reactions on skin testing than Comparisons. The unadjusted analyses of the laboratory examination data indicated no significant group difference between Ranch Hands and Comparisons. For the adjusted analyses of the natural killer assay measurements with and without Interleukin 2 (IL-2), significant interactions between group and race were present. The clinical significance of these findings is not apparent and does not point to any known clinical endpoints. In general, the immunologic assessment revealed no medically important differences between Ranch Hands and Comparisons.

Serum Dioxin Analysis of 1987 Followup Study Summary Results

In general, the composite skin test diagnosis results were not associated with serum dioxin levels. The Ranch Hand analyses using initial dioxin, and the analyses using current dioxin and time since duty in Southeast Asia (SEA), generally displaying nonsignificant decreased risks. For the analyses contrasting Ranch Hands with unknown, low, and high current dioxin to Comparisons with background current dioxin levels, the risks were increased but nonsignificant.

For the most part, the cell surface marker variables and TLC did not display significant associations with serum dioxin. The longitudinal analyses of the CD4-CD8 ratio did not consistently show significant differences in the 1987 ratio relative to the 1985 measurement of the ratio.

For the analyses of PHA net responses, significant or marginally significant positive associations with initial dioxin were found. For the analyses involving current dioxin and time since duty in SEA, the maximum PHA net response also displayed some significant or marginally significant positive associations. Depressed immune function would be expected to demonstrate lower PHA net response.

For unstimulated MLC and MLC net response, the three analysis approaches generally displayed nonsignificant associations with serum dioxin. For the analysis involving Ranch Hands in the high current dioxin category and Comparisons in the background current dioxin category, Ranch Hands had a significantly higher unstimulated MLC mean. The analyses of the natural killer cell variables generally were nonsignificant.

Significant positive associations generally were found between IgA and initial dioxin. The analyses for IgA, IgG, and IgM using current dioxin and time since duty in SEA were, for the most part, nonsignificant. For the three immunoglobulins, the overall contrasts of Ranch Hands in the unknown, low, and high current dioxin categories versus Comparisons in the background current dioxin category generally were significant or marginally significant. For IgA and IgG, the contrasts of Ranch Hands in the unknown current dioxin category versus Comparisons in the background current dioxin category were significant with Ranch Hands having lower immunoglobulin averages. For IgM, the contrasts of Ranch Hands in the low current dioxin category versus Comparisons in the background current dioxin category were marginally significant with Ranch Hands again having lower averages. Ranch Hands in the high dioxin category were not significantly different from Comparisons.

The indices of immune responses analyzed in the 1987 examination provided a comprehensive reflection of in vivo and in vitro immune function in the study population. No clinically significant indicators reflecting a relationship between the current body burden of dioxin or the extrapolated initial exposure and immune function were found. Similar to elevated erythrocyte sedimentation rates (in the General Health Assessment) and increased white blood cell and platelet counts (in the Hematologic Assessment), increased IgA levels could represent a chronic inflammatory response to dioxin exposure.

Parameters for the Immunologic Assessment

Dependent Variables

Data from the physical examination, the Scripps Clinic and Research Foundation (SCRF) laboratory, and the Scripps Immunology Reference Laboratory (SIRL) were used in the Immunologic Assessment. The skin testing, immunoglobulin studies, and lupus panel tests were examined for all participants, whereas the cell surface marker studies and total lymphocyte count (TLC) investigations were carried out on a random sample of approximately 40 percent of the participants, because of the complexity of the assay and the expense of the tests.

Physical Examination Data

Physical examination data concerning the skin tests were used to evaluate immunologic function. A composite skin test diagnosis variable was constructed based on the responses to four separate antigens injected intradermally to measure antigen reactivity or sensitivity. This composite skin test variable was analyzed as a discrete, dichotomous variable; each participant was considered possibly abnormal or normal based on his skin reactivity to the antigens *Candida albicans*, mumps, Trichophyton, and staph-phage lysate. The response to each antigen was scored positive (normal) if the maximum diameter of the resulting 48-hour induration was greater than or equal to 5 millimeters (mm), which indicates intact cell-mediated immunity. If none of the four antigen responses was positive, the composite skin test diagnosis was scored possibly abnormal. If one or more of the four antigen responses were positive, the composite skin test was considered normal.

Participants who were taking anti-inflammatory medication (except aspirin) or immunosuppressant medication at the time of the 1992 physical examination, participants who recently received x ray treatment or chemotherapy for cancer (reported in the 1992 questionnaire and verified by medical records review), and participants who tested positive for HIV were excluded from all analyses of skin test data.

Laboratory Examination Data

From the SCRF and SIRL immunologic tests, the results of cell surface marker studies, TLC, quantitative immunoglobulins, and a lupus panel were analyzed. Table 19-1 presents the immunologic parameters evaluated and describes their medical importance. Continuous data were evaluated statistically to determine whether the natural logarithm scale was more

Table 19-1.
Medical Significance of the Immunologic Data

Immunologic Measure	Rationale of the Measurement	Disease/Syndrome/Condition Endpoint
Skin Tests		
Candida Mumps Trichophyton Staph-phage lysate	Skin testing measures in vivo hypersensitivity responses to antigens of bacteria, fungi, and a virus to which most persons have previously been exposed. The skin reaction to intradermal injection of these antigens indicates integrity of T-cell memory and ability of effector cells to mount a response.	Antigen reactivity or sensitivity. Lack of response to all antigens indicates anergy that may occur in overwhelming infections, widespread malignancy, immunosuppression, or malnutrition.
Cell Surface Marker Studies		
CD3	Pan T-cell marker (similar to CD2) in previous study cycle). Measures all mature T cells (includes CD4, CD8, etc.). Generally 70% or more of peripheral blood lymphocytes are CD3 positive.	Decrease in absolute number of T cells indicates immunodeficiency. May occur due to direct effects of malignancy (e.g., lymphoma), to AIDS, or to chemotherapy. Increase may occur in lymphoproliferative disorders or in some infections.
CD4 (Lue3a+b)	Measures T cells that exhibit helper/inducer phenotype. CD4 cells initiate an immune response to processed antigens.	Markedly decreased in AIDS due to HIV infection of CD4+ cells; increased in autoimmune diseases.
CD5	Marker expressed by T cells; also found on subpopulation of B cells.	B-cell type of chronic lymphocytic leukemia expresses CD5; lymphocytes involved in autoimmune disease frequently express CD5.
CD8 (OKT8)	Measures T cells that exhibit suppressor and cytotoxic functions. Responsible for appropriate down regulation of an immune response after antigen has been cleared.	Variable in autoimmune diseases; increased in some viral illnesses and immunodeficiencies.
CD14 (LeuM3)	Measures mature monocytes in peripheral blood. Monocytes take up and process foreign antigens for presentation to CD4+ cells.	Increases with inflammation of many etiologies.
CD16+56	Measures natural killer (NK) cells that can lyse foreign cells independent of antibody or prior contact with the target. CD16 is an IgG receptor that appears on NK cells and neutrophils; CD56 is more restricted to NK cells; joint use of CD16 and CD56 enhances enumeration of NK cells.	NK cells are thought to attack neoplasms and naturally prevent growth of cancers.

Table 19-1. (Continued)
Medical Significance of the Immunologic Data

Immunologic Measure	Rationale of the Measurement	Disease/Syndrome/Condition Endpoint
CD20 (B1)	Measures peripheral blood B cells; no reaction with T cells, granulocytes, or monocytes.	Decreased result in humoral immune deficiency with impaired production of antibodies; increased in lymphoproliferative disorders.
CD25 (IL-2 Receptor)	Present on activated T cells; absent on normal peripheral blood lymphocytes, monocytes, and granulocytes. Stimulation with IL-2 induces more IL-2 Receptor synthesis in activated T cells (positive feedback).	Increased in lymphoproliferative disorders. Also increased with any immune activation (viral infection, organ transplant rejection).
CD4-CD8 Ratio	Measures proportional difference between CD4+ cell populations and CD8+ cell populations. Reflects balance between up regulation and down regulation of T cells.	Decreased in immunodeficiencies and viral illnesses. AIDS causes very low ratio, as does immunosuppression with cyclosporine.
Double Labelled Cells (cells that express both markers)		
CD3 with CD25	More refined measurement of activated T cells to avoid possible (minor) inclusion of other cell types expressing CD25.	Same as CD25.
CD5 with CD20	T cell marker (CD5) with B cell marker (CD20) on same lymphocytes indicates abnormal cell subpopulation.	These doubly positive cells occur as a major population in chronic lymphocytic leukemia; as a minor population, they can indicate lymphocytes responsible for autoimmune processes.
CD4 with CD8	Normally these markers do not occur on the same cells.	Doubly positive cells indicate primitive lymphocytes suggesting abnormal T cell clone or leukemia.
CD3 with (CD16 + CD56)	Normally these markers do not occur on the same cells.	Same as CD16 plus CD56.
Total Lymphocyte Count	Measures absolute number of total lymphocytes circulating in peripheral blood. Major immune mechanism against fungi and viruses.	Decreased in immunodeficiency; increased in lymphoproliferative disorders.

Table 19-1. (Continued)
Medical Significance of the Immunologic Data

Immunologic Measure	Rationale of the Measurement	Disease/Syndrome/Condition Endpoint
Immunoglobulins IgG IgA IgM	Each measures ability of specific B-cell subgroup to secrete specific antibody class of molecules. Antibodies normally rise in response to infections or immunizations with bacteria, fungi, and viruses. Major immune mechanism against bacteria.	Increased in hyperglobulinemia or myeloma (monoclonal). Decreased in selective or total B-cell immunodeficiency. Polyclonal increases in chronic inflammation and liver disease (cirrhosis).
Lupus Panel	The test composition of this profile was chosen to include the most frequently encountered autoantibodies. Presence of autoantibodies may indicate specific autoimmune diseases, especially if multiple autoantibodies are present. The individually named autoantibodies (excluding ANA and B cell clones) are associated with specific diseases. Any of these tests also may turn positive as a participant's immune system ages or otherwise is dysregulated.	
Antinuclear Antibody (ANA) Test	Screening assay (performed with monolayers of HEp-2) for many clinically significant autoantibodies that occur in systemic rheumatologic diseases; all positives were further tested by confirmatory assays for specific autoantibodies against: DNA, Sm, RNP, SS-A, SS-B.	Positive result suggests possible rheumatologic disease; likelihood increases with number of different positive autoantibodies.
Thyroid Microsomal Antibody	Measures autoantibodies against thyroid.	Present in autoimmune thyroiditis.
MSK Smooth Muscle Antibody	MSK indicates the tissues used in the assay (mouse stomach and kidney); measures autoantibodies against actin in smooth muscle.	Present in autoimmune liver diseases, especially chronic active hepatitis.
MSK Mitochondrial Antibody	Measures autoantibodies against mitochondrial antigens.	Present in autoimmune liver diseases, especially biliary cirrhosis.
MSK Parietal Antibody	Measures autoantibodies against parietal cells of the stomach that make intrinsic factor for the absorption of vitamin B_{12}.	Present in pernicious anemia (failure to absorb vitamin B_{12}).
Rheumatoid Factor	Autoantibodies reactive with a person's own antibodies.	Present in rheumatoid arthritis; also in some infections, chronic pulmonary diseases, and other inflammatory or autoimmune diseases.

Table 19-1. (Continued)
Medical Significance of the Immunologic Data

Immunologic Measure	Rationale of the Measurement	Disease/Syndrome/Condition Endpoint
B Cell Clones Detected by Serum Protein Electrophoresis	Detection of monoclonal immunoglobulins by serum protein electrophoresis. Normal immunoglobulins are polyclonal with no predominant single clone. All positive results were further tested for heavy chain type (G, A, M) and light chain type (kappa, lambda).	Large amounts of monoclonal immunoglobulins are present in multiple myeloma and other lymphoproliferative disorders; also can occur in smaller amounts in aging or dysregulated immune systems.
Other Antibodies	May be detected incidentally in performance of the above assays, may not be clinically significant except as indicator of immune system aging or dysfunction.	
Summary Index	General measure of the integrity of the immune system, specifically as it affects B cells.	

appropriate to use with the statistical procedure(s) than the original scale. Participants who were taking anti-inflammatory medication (except aspirin) or immunosuppressant medication at the time of the 1992 physical examination, participants who had recently received x ray treatment or chemotherapy for cancer, and participants who tested positive for HIV were excluded from all analyses of the laboratory data.

Cell Surface Marker (Phenotypic) Studies—Quantification of the different cell populations was carried out with the use of reagent mouse monoclonal antibodies. Eight cell surface markers, one ratio of cell markers, and four double-labelled cell surface markers were analyzed in the statistical evaluation of the immunologic system. The unit of measurement (for all variables except the ratio) was cells/mm^3.

A substantial number of participants had measurements of 0 cells/mm^3 for the double-labelled cell surface markers CD5 with CD20, CD4 with CD8, and CD3 with CD16+56. The distribution of these double labelled cell surface markers were skewed, suggesting the need for a logarithmic transformation. Consequently two sets of analyses were done on each variable. Analyses were performed on the nonzero values in their continuous form incorporating a logarithmic transformation. A second analysis was done on each variable, relating the percentage of zero measurements to the estimate of exposure.

Total Lymphocyte Count (TLC)—The TLC indicates the density of lymphocytes in the blood. Lymphocytes recognize and destroy bacteria, fungi, viruses, and other foreign bodies. Statistical analysis was performed on TLC, as measured in cells/mm^3.

Immunoglobulins—Immunoglobulins measure the ability of a specific B-cell subgroup to secrete a specific antibody class of molecules. The antibodies typically rise in response to infections or immunizations with bacteria, fungi, and viruses. Statistical analysis was performed on the immunoglobulins IgA, IgG, and IgM, measured in mg/dl.

Lupus Panel—This group of laboratory tests was configured to detect the most frequent autoantibodies found in both patients and asymptomatic individuals. Autoantibodies are markers for autoimmune diseases, and the lupus panel is considered a screening assay for a wide spectrum of autoimmune disorders (e.g., rheumatoid arthritis, systemic lupus erythematosus). Occasionally, autoantibodies are detected in asymptomatic persons; this is alternatively explained as evidence for incipient autoimmune disease or a finding of unknown clinical significance. In any instance, the finding of an autoantibody is not normal and should be interpreted as an aberration of the immune system. The lupus panel was composed of the following individual tests on serum:

- **Antinuclear antibody (ANA)** performed on HEP-2 cells. Positive results are expressed as:
  - Titer (e.g., 1:40, 1:160)
  - Pattern (e.g., speckled, homogeneous, centromere, nucleolar, other ANA).

If the ANA was negative, no further specific antibody assays were performed. If the ANA was positive, the following major specific antibody measurements were performed:
- DNA
- Sm
- RNP
- SS-A
- SS-B.

- **Mouse stomach kidney (MSK) section stain** for the following specific autoantibodies:
  - Smooth muscle
  - Mitochondrial
  - Parietal cell
  - Other MSK.

- **Thyroid microsomal antibody**

- **Rheumatoid factor.**

All of the autoantibodies derive from abnormalities of the B-cell portion, the part of the immune system that makes immunoglobulins.

Statistical analyses were performed on the ANA, MSK smooth muscle antibody, MSK mitochondrial antibody, MSK parietal cell antibody, thyroid microsomal antibody, rheumatoid factor, B-cell clones detected by serum protein electrophoresis, and other ANA and MSK antibodies, with the response to these tests scored as present or absent. The B-cell clones as detected by serum electrophoresis are a composite of 11 subtests and are considered present if any bands from the subtests are present. Statistical analyses also were performed on a lupus panel summary index, which was constructed from the eight individual tests and scored as "abnormal" if any of the eight individual tests were abnormal and "normal" if all eight tests were normal.

The test for B-cell clones performed by high resolution electrophoresis and immunofixation on serum is one additional measure of B-cell abnormality. High resolution electrophoresis for detection of monoclonal bands is not formally part of the lupus panel because such antibody bands are not necessarily autoantibodies. However, both autoantibodies and monoclonal bands are evidence for derangement of the B-cell portion of the immune system. For that reason, it is appropriate to include the B-cell clone test results with the lupus panel autoantibody results in a composite summary index of B-cell abnormalities.

Covariates

Covariates used in the immunologic evaluation for adjusted statistical analyses include age, race, military occupation, current alcohol use (drinks/day), lifetime alcohol history (drink-years), current cigarette smoking (cigarettes/day), lifetime cigarette smoking history

(pack-years), and exercise history (an index combining both duration and intensity). Further, batch-to-batch (examination group) variation also was used as a covariate for the cells surface maker (phenotypic) studies and TLC. Study participants who began their physical examination on the same day form a batch.

Lifetime alcohol history was based on self-reported information from the 1992 questionnaire and combined with similar information gathered at the 1987 followup. The respondent's average daily alcohol consumption was determined for various drinking stages throughout his lifetime, and an estimate of the corresponding total number of drink-years (1 drink-year is the equivalent of drinking 1.5 ounces of 80-proof alcoholic beverage per day for 1 year) was derived. The current alcohol covariate was based on the average drinks per day for the month prior to completing the questionnaire.

Current cigarette smoking and lifetime cigarette smoking history were based on self-reported questionnaire data. For lifetime cigarette smoking history, the respondent's average smoking was estimated over his lifetime, assuming 365 packs of cigarettes equal 1 pack-year.

A series of questions concerning exercise patterns in the past 2 weeks were added to the AFHS and incorporated in the 1992 questionnaire. The participants were asked questions on frequency, average duration per frequency, and increase of heart rate or breathing for over 20 different activities. The answers to these questions were used and combined to determine an index of physical activity incorporating duration and intensity (50,51), and this covariate was used in adjusted statistical analyses.

Statistical Methods

Chapter 7, Statistical Methods, describes most of the basic statistical methods used in the Immunologic Assessment. For both the 1985 and the 1987 studies, large variation was expected from batch variability. Because of the variation, this covariate was generally incorporated into the unadjusted and the adjusted models of the respective Immunologic Assessments for the 1985 and 1987 studies. For the analyses of the cell surface markers and TLC, the batch-to-batch covariate was subject to a prescreening procedure to determine whether the unadjusted and adjusted models should incorporate this covariate. The prescreening was performed because of the reduced sample sizes available for the stepwise modeling procedure applied to those models involving only the Ranch Hands. In addition, the batch-to-batch covariate absorbs many of the available degrees of freedom if routinely forced into a particular analysis model.

To address the issues regarding reduced sample sizes and decreased degrees of freedom, a main effects prescreening model with the following terms was used for the cell surface markers and TLC: group, batch-to-batch variation, age, race, occupation, current alcohol use, lifetime alcohol history, current cigarette smoking, lifetime cigarette smoking history, and exercise history index. The models were used to evaluate the significance of the batch-to-batch covariate using the data from the group analysis (the largest data set of the 6 models). As a result of that analysis, the batch-to-batch covariate was used for the unadjusted and adjusted analyses of the following cell surface markers: CD3, CD4, CD5,

CD14, CD16+56, CD25, CD3 with CD25, CD5 with CD20, CD3 with CD16+56, and TLC. Batch-to-batch variation was not used in the unadjusted and adjusted analyses of CD8, CD20, CD4-CD8 ratio, and CD4 with CD8.

Table 19-2 summarizes the statistical analyses performed for the analysis of the Immunologic Assessment. The first part of the table describes the dependent variables analyzed. The second part of the table further describes the candidate covariates examined. Abbreviations used in the body of the table are defined at the end of the table. Some participants were excluded from the immunologic evaluation as stated previously, and some dependent variable and covariate data were missing for other participants. Table 19-3 summarizes the number of participants excluded for medical reasons and the number of participants with missing data. Variables used to evaluate skin, immunologic testing, and the lupus panel tests are detailed separately in this table, because different subsets of participants received these types of tests.

Analyses of data collected at the 1987 followup study indicated that dioxin was associated with military occupation. In general, enlisted personnel had higher levels of dioxin than officers, with enlisted groundcrew having higher levels than enlisted flyers. Consequently, adjustment for military occupation in statistical models using dioxin as a measure of exposure may improperly mask an actual dioxin effect. However, occupation also can be a surrogate for socioeconomic effects. Failure to adjust for occupation could overlook important risk factors related to lifestyle. If occupation was found to be significantly associated with a dependent variable in the 1992 followup analyses and was retained in the final statistical models using dioxin as a measure of exposure, the dioxin effect was evaluated in the context of two models. Analyses were performed with and without occupation in the final models to investigate whether conclusions regarding the association between the health endpoint and dioxin differed.

The results of the analyses without occupation are presented in Appendix O-3 and are only discussed in the text if the level of significance differs from the original final adjusted model (significant versus nonsignificant).

Longitudinal Analyses

Longitudinal analyses were performed on the CD4-CD8 ratio using the data collected for the 1985 and 1992 examinations to assess the association between exposure and the change in this ratio between the two examinations. See Chapter 7, Statistical Methods, for a further discussion of methods used in the longitudinal analyses.

Table 19-2.
Statistical Analyses for the Immunologic Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Composite Skin Test Diagnosis (based on length of four skin test antigen induration measurements)	PE	D	Possibly Abnormal: 0/4 ≥5 mm Normal: ≥1/4 ≥5 mm	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT	U:LR,CS A:LR
CD3 Cells (cells/mm^3)	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT,BATCH	U:GLM A:GLM
CD4 Cells (cells/mm^3)	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT,BATCH	U:GLM,TT A:GLM
CD5 Cells (cells/mm^3)	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT,BATCH	U:GLM,TT A:GLM
CD8 Cells (cells/mm^3)	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT,BATCH	U:GLM,TT A:GLM
CD14 Cells (cells/mm^3)	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT,BATCH	U:GLM A:GLM
CD16+56 Cells (cells/mm^3)	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT,BATCH	U:GLM A:GLM
CD20 Cells (cells/mm^3)	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT,BATCH	U:GLM,TT A:GLM
CD25 Cells (cells/mm^3)	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT,BATCH	U:GLM A:GLM

Table 19-2. (Continued)
Statistical Analyses for the Immunologic Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
CD4-C8 Ratio	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT,BATCH	U:GLM,TT A:GLM L:GLM,TT
Double Labelled Cells: CD3 with CD25 (cells/mm^3)	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT,BATCH	U:GLM A:GLM
Double Labelled Cells: CD5 with CD20 (cells/mm^3)	LAB	D/C	Zero Nonzero	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT,BATCH	U:LR,CS, GLM,TT A:LR,GLM
Double Labelled Cells: CD4 with CD8 (cells/mm^3)	LAB	D/C	Zero Nonzero	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT,BATCH	U:LR,CS, GLM,TT A:LR,GLM
Double Labelled Cells: CD3 with CD16+56 (cells/mm^3)	LAB	D/C	Zero Nonzero	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT,BATCH	U:LR,CS, GLM,TT A:LR,GLM
Total Lymphocyte Count (TLC) (cells/mm^3)	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT,BATCH	U:GLM A:GLM
IgA (mg/dl)	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT	U:GLM A:GLM
IgG (mg/dl)	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT	U:GLM A:GLM
IgM (mg/dl)	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT	U:GLM A:GLM
Lupus Panel: ANA Test	LAB	D	Present Absent	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT	U:LR,CS A:LR

Table 19-2. (Continued)
Statistical Analyses for the Immunologic Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Lupus Panel: ANA Thyroid Microsomal Antibody	LAB	D	Present Absent	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT	U:LR,CS A:LR
Lupus Panel: MSK Smooth Muscle Antibody	LAB	D	Present Absent	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT	U:LR,CS A:LR
Lupus Panel: MSK Mitochondrial Antibody	LAB	D	Present Absent	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT	U:LR,CS A:LR
Lupus Panel: MSK Parietal Antibody	LAB	D	Present Absent	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT	U:LR,CS A:LR
Lupus Panel: Rheumatoid Factor	LAB	D	Present Absent	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT	U:LR,CS A:LR
Lupus Panel: B Cell Clones Detected by Serum Protein Electrophoresis	LAB	D	Present Absent	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT	U:LR,CS A:LR
Lupus Panel: Other Antibodies (ANA and MSK)	LAB	D	Present Absent	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT	U:LR,CS A:LR
Lupus Panel: Summary Index	LAB	D	Abnormal Normal	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT	U:LR,CS A:LR

Table 19-2. (Continued)
Statistical Analyses for the Immunologic Assessment

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Age (AGE)	MIL	D/C	Born≥1942 Born<1942
Race (RACE)	MIL	D	Black Non-Black
Occupation (OCC)	MIL	D	Officer Enlisted Flyer Enlisted Groundcrew
Current Cigarette Smoking (CSMOK) (cigarettes/day)	Q-SR	D/C	0-Never 0-Former >0-20 >20
Lifetime Cigarette Smoking History (PACKYR) (pack-years)	Q-SR	D/C	0 >0-10 >10
Current Alcohol Use (ALC) (drinks/day)	Q-SR	D/C	0-1 >1-4 >4
Lifetime Alcohol History (DRKYR) (drink-years)	Q-SR	D/C	0 >0-40 >40
Physical Activity Index (PHYACT) (kcal/kg/day)	Q-SR	D	Sedentary: <1.45 Moderate: 1.45-<2.95 Very Active: ≥2.95
Batch-to-Batch (BATCH)	LAB	D	1, 2, 3, ... 81

Abbreviations

Data Source:
- LAB = 1992 SCRF laboratory and SIRL results
- MIL = Air Force Military Records
- PE = 1992 physical examination
- Q-SR = Health questionnaires (self-reported)

Data Form:
- D = Discrete analysis only
- C = Continuous analysis only
- D/C = Discrete and continuous analyses for dependent variables; appropriate form for analysis (either discrete or continuous) for covariates

Statistical Analyses:
- U = Unadjusted analyses
- A = Adjusted analyses
- L = Longitudinal analyses

Table 19-3.
Number of Participants with Missing Data for, or Excluded from, the Immunologic Assessment

Variable	Variable Use	Group: Ranch Hand	Group: Comparison	Dioxin (Ranch Hands Only): Initial	Dioxin (Ranch Hands Only): Current	Categorized Dioxin: Ranch Hand	Categorized Dioxin: Comparison
Skin Test Analysis[a]							
Composite Skin Test Diagnosis	DEP	20	46	7	17	17	32
Chemotherapy or X Ray Treatment	EXC	2	4	2	2	2	3
Anti-Inflammatory or Immunosuppressant Medication	EXC	11	11	5	11	11	8
HIV Positive	EXC	3	1	2	3	3	1
Immunologic Test Analyses[b]							
CD3 Cells	DEP	1	0	1	1	1	0
CD4 Cells	DEP	1	0	1	1	1	0
CD5 Cells	DEP	1	0	1	1	1	0
CD8 Cells	DEP	1	0	1	1	1	0
CD14 Cells	DEP	1	0	1	1	1	0
CD16+56 Cells	DEP	1	0	1	1	1	0
CD20 Cells	DEP	1	0	1	1	1	0
CD25 Cells	DEP	1	0	1	1	1	0
CD4-CD8 Ratio	DEP	1	0	1	1	1	0
Double Labelled Cells: CD3 with CD25	DEP	1	0	1	1	1	0
Double Labelled Cells: CD5 with CD20	DEP	1	0	1	1	1	0
Double Labelled Cells: CD4 with CD8	DEP	1	0	1	1	1	0
Double Labelled Cells: CD3 with CD16+56	DEP	1	0	1	1	1	0
Total Lymphocyte Count	DEP	1	0	1	1	1	0

Table 19-3. (Continued)
Number of Participants with Missing Data for, or Excluded from, the Immunologic Assessment

		Group		Dioxin (Ranch Hands Only)		Categorized Dioxin	
Variable	Variable Use	Ranch Hand	Comparison	Initial	Current	Ranch Hand	Comparison
Chemotherapy or X Ray Treatment	EXC	1	3	0	1	1	3
Anti-Inflammatory or Immunosuppressant Medication	EXC	4	5	3	4	4	5
HIV Positive	EXC	0	1	0	0	0	1
Lupus Panel and Quantitative Immunoglobins[a]							
Lupus Panel: ANA Test	DEP	0	1	0	0	0	0
Lupus Panel: Thyroid Microsomal Antibody	DEP	0	1	0	0	0	0
Lupus Panel: MSK Smooth Muscle Antibody	DEP	0	1	0	0	0	0
Lupus Panel: Mitochondrial Antibody	DEP	0	1	0	0	0	0
Lupus Panel: MSK Parietal Antibody	DEP	0	1	0	0	0	0
Lupus Panel: Rheumatoid Factor	DEP	0	1	0	0	0	0
Lupus Panel: B Cell Clones Detected by Serum Protein Electrophoresis	DEP	0	1	0	0	0	0
Lupus Panel: Other Antibodies	DEP	4	4	2	4	4	3
Lupus Panel: Summary Index	DEP	3	2	2	3	3	1
IgG	DEP	0	1	0	0	0	0
IgA	DEP	0	1	0	0	0	0
IgM	DEP	0	1	0	0	0	0

Table 19-3. (Continued)
Number of Participants with Missing Data for, or Excluded from, the Immunologic Assessment

		Group		Dioxin (Ranch Hands Only)		Categorized Dioxin	
Variable	Variable Use	Ranch Hand	Comparison	Initial	Current	Ranch Hand	Comparison
Chemotherapy or X Ray Treatment	EXC	2	4	2	2	2	3
Anti-Inflammatory or Immunosuppressant Medication	EXC	11	11	5	11	11	8
HIV Positive	EXC	3	1	2	3	3	1
Covariates							
Current Cigarette Smoking	COV	0	2	0	0	0	2
Lifetime Cigarette Smoking History	COV	1	2	0	1	1	2
Current Alcohol Use	COV	10	18	7	9	9	16
Lifetime Alcohol History	COV	22	21	13	20	20	18
Physical Activity Index	COV	0	2	0	0	0	2

[a]Performed on 952 Ranch Hands and 1,281 Comparisons.
[b]Performed on 373 Ranch Hands and 491 Comparisons.

Abbreviations: DEP = Dependent variable (missing data).
COV = Covariate (missing data).
EXC = Exclusion.

One Ranch Hand missing total lipids for current dioxin.

RESULTS

Dependent Variable-Covariate Associations

Appendix Table O-1-1 presents the results of the following tests of association between immunology variables and covariates.

The composite skin test variable was based on the response to four separate antigens injected intradermally to measure antigen reactivity or sensitivity increased significantly with age ($p=0.014$) and lifetime cigarette smoking history ($p=0.014$). Non-Black participants had a significantly higher percentage of abnormal composite skin test results than Black participants ($p=0.048$).

The cell surface marker analysis of CD3 cells showed that the number of CD3 cells decreased with age ($p=0.045$) and increased with current cigarette smoking ($p<0.001$) and lifetime cigarette smoking history ($p<0.001$). The number of CD3 cells were higher for enlisted flyers and enlisted groundcrew than for officers ($p=0.030$).

Similarly, analysis of CD4 cells revealed that the number of CD4 cells decreased with age ($p=0.002$). Mean CD4 cell counts increased as current cigarette smoking and lifetime cigarette smoking history increased among participants ($p<0.001$ for both analyses).

Examination of CD5 cells showed a decrease with age ($p=0.008$) and an increase with current cigarette smoking ($p<0.001$) and lifetime cigarette smoking history ($p=0.001$). The enlisted groundcrew had the highest mean CD5 cell count followed by the enlisted flyers and then officers ($p=0.037$).

The mean CD8 cell count increased as current cigarette smoking ($p<0.001$) and lifetime cigarette smoking history ($p=0.044$) increased among participants.

Analysis of CD14 cells revealed non-Black participants had a higher mean CD14 cell count than Black participants ($p=0.005$). The number of CD14 cells increased with age ($p=0.050$), current cigarette smoking ($p<0.001$), lifetime cigarette smoking history ($p<0.001$), and lifetime alcohol history ($p=0.001$). Moderately active participants had the highest mean CD14 cell value followed by sedentary participants and then very active participants ($p=0.025$).

Analysis of CD16+56 cells displayed a significant positive association between CD16+56 cells and age ($p=0.010$) and a significant inverse relationship with current cigarette smoking ($p=0.003$).

CD20 cell counts increased significantly with age ($p<0.001$) and current cigarette smoking ($p<0.001$). Black participants had a significantly higher mean CD20 cell count than non-Black participants ($p=0.047$), and enlisted groundcrew had the highest mean CD20 cell counts followed by enlisted flyers and then officers ($p<0.001$).

CD25 cell counts decreased with age (p=0.002) and increased with current cigarette smoking (p<0.001), lifetime cigarette smoking history (p<0.001), and current alcohol use (p=0.034) among participants. Enlisted groundcrew had the highest mean CD25 values followed by enlisted flyers and then officers (p=0.047).

Analysis of the CD4-CD8 ratio exhibited a significant negative association with age (p<0.001) and a significant positive association with current cigarette smoking (p=0.002).

The double labelled cell surface marker analysis of CD3 with CD25 demonstrated a significant inverse association with age (p=0.005) and positive associations with current cigarette smoking (p<0.001), lifetime cigarette smoking history (p<0.001), and current alcohol use (p=0.035). Enlisted groundcrew had the highest mean CD3 with CD25 cell count followed by enlisted flyers and then officers (p=0.035).

The double labelled cell surface marker CD5 with CD20 contained many measurements of 0 cells/mm^3. Analyses were performed on the nonzero values in their continuous form as well as dichotomized as zero and nonzero. The analysis of nonzero CD5 with CD20 measurements revealed a significant inverse relationship with age (p<0.001), lifetime cigarette smoking history (p=0.009), current alcohol use (p<0.001), and lifetime alcohol history (p=0.009). Enlisted groundcrew had the highest mean CD5 with CD20 level followed by the enlisted flyers and then officers (p=0.001). The analysis of CD5 with CD20 in its dichotomized form showed that the prevalence of zero values increased significantly with current alcohol use (p=0.038).

Similarly, two analyses were performed on the double labelled cell surface marker CD4 with CD8 due to the presence of 0 cells/mm^3 measurements. The analysis performed on the nonzero CD4 with CD8 measurements revealed a significant positive relationship with current cigarette smoking (p<0.001). The analysis of CD4 with CD8 when categorized as zero or nonzero revealed a higher percentage of the younger participants with no CD4 with CD8 cells present (p=0.037).

Both discrete (zero vs. nonzero) and continuous (nonzero measurements only) analyses were performed on double labelled CD3 with CD16+56 cells. The analysis of nonzero CD3 with CD16+56 cells revealed a significant positive relationship with age (p<0.001). The analysis of the nonzero CD3 with CD16+56 cell showed Black participants had a higher mean CD3 with CD16 cell count than non-Black participants (p<0.001).

TLC decreased with age (p=0.005) and increased with current cigarette smoking (p<0.001) and lifetime cigarette smoking history (p<0.001). The enlisted groundcrew had the highest mean TLC followed by enlisted flyers and officers (p=0.002).

The immunoglobulin IgA increased significantly with age (p=0.002) and lifetime alcohol history (p=0.031).

Black participants had a significantly higher mean level of the immunoglobulin IgG than non-Black participants (p<0.001). IgG decreased with current cigarette smoking (p<0.001), lifetime cigarette smoking history (p<0.001), current alcohol use (p=0.016),

and lifetime alcohol history ($p=0.039$). The enlisted groundcrew had the highest mean IgG level followed by enlisted flyers and officers ($p=0.002$).

The mean levels of the immunoglobulin IgM decreased with age ($p=0.002$) and increased with current alcohol use ($p=0.026$). Mean IgM levels were higher in non-Black participants than in Black participants ($p=0.003$).

Older participants had a significantly higher percentage of abnormal results in the lupus panel antinuclear antibody (ANA) test ($p<0.001$), the mouse stomach kidney (MSK) smooth muscle antibody test ($p=0.008$), and the rheumatoid factor ($p=0.002$) than the younger participants.

The analysis of B cell clones detected by serum protein electrophoresis revealed an increase in positive results with age ($p=0.024$) and lifetime cigarette smoking history ($p=0.012$). Enlisted flyers had the highest percentage of positive results followed by officers and enlisted groundcrew ($p=0.033$). Participants who smoked between 0 and 20 cigarettes per day had the highest percentage of B cell clones detected, followed by those who formerly smoked, those who smoke 20 or more cigarettes per day, and those who have never smoked ($p=0.006$).

The lupus panel summary index was constructed from the eight individual tests and scored as abnormal if any of the eight individual tests were abnormal and normal if all eight tests were normal. Older participants had a higher percentage of an abnormal summary index than the younger participants ($p<0.001$). Officers had the highest percentage of abnormal findings in the summary index followed by enlisted flyers and then enlisted groundcrew ($p=0.009$).

Exposure Analysis

The following section presents the results of the statistical analyses of the dependent variables shown in Table 19-2. Dependent variables are grouped into two sections: one variable obtained during the 1992 physical examination and data derived from the immunology laboratory portion of the 1992 followup examination.

Unadjusted and adjusted analyses of six models are presented for each variable. Model 1 examines the relationship between the dependent variable and group (Ranch Hand or Comparison). Model 2 explores the relationship between the dependent variable and an extrapolated initial dioxin measure for Ranch Hands who had a 1987 dioxin measurement greater than 10 ppt. If a participant did not have a 1987 dioxin level, a 1992 level was used. A statistical adjustment for the percent of body fat at the participant's time of duty in SEA and the change in the percent of body fat from the time of duty in SEA to the date of the blood draw for dioxin is included in this model to account for body-fat-related differences in elimination rate (52). Model 3 dichotomizes the Ranch Hands in Model 2 based on their initial dioxin measures; these two categories of Ranch Hands are referred to as the "low Ranch Hand" category and the "high Ranch Hand" category. These participants are added to Ranch Hands and Comparisons with current serum dioxin levels (1987, if available; 1992, if the 1987 level was not available) at or below 10 ppt to create a total of four categories.

Ranch Hands with current serum dioxin levels at or below 10 ppt are referred to as the "background Ranch Hand" category. The relationship between the dependent variable in each of the three Ranch Hand categories and the dependent variable in the "Comparison" category is examined. A fourth contrast, exploring the relationship of the dependent variable in the low Ranch Hand category and the high Ranch Hand category combined, also is conducted. This combination is referred to in the text and tables as the "low plus high Ranch Hand" category. As in Model 2, a statistical adjustment is made for the percent of body fat at the participant's time of duty in SEA and the change in the percent of body fat from the time of duty in SEA to the date of the blood draw for dioxin.

Models 4, 5, and 6 examine the relationship between the dependent variable and 1987 dioxin levels in all Ranch Hands with a dioxin measurement. If a participant did not have a 1987 dioxin measurement, a 1992 measurement was utilized in determining the current dioxin level. The measure of dioxin in Model 4 is lipid-adjusted, whereas whole-weight dioxin is used in Models 5 and 6. Model 6 differs from Model 5 in that a statistical adjustment for total lipids is included in Model 6. Further details on dioxin and the modeling strategy are found in Chapters 2 and 7 respectively.

Results of investigation for group-by-covariate and dioxin-by-covariate interactions are referenced in the text, and tabular results are presented in Appendix O-2. As described previously, additional analyses were performed when occupation was retained in the final models for Models 2 through 6. Results excluding occupation from these models are tabled in Appendix O-3, and dioxin-by-covariate interactions with occupation excluded from these models are presented in Appendix O-4. Results from analyses excluding occupation are discussed in the text only if a meaningful change occurred (that is, changes between significant results, marginally significant results, and nonsignificant results).

Physical Examination Variable

Composite Skin Test Diagnosis

A composite skin test diagnosis was constructed based on the response to four separate antigens injected intradermally to measure antigen reactivity or sensitivity. If none of the four antigen responses were positive, the composite skin test diagnosis was scored "possibly abnormal." If one or more of the four antigen responses was positive, the composite skin test was considered "normal."

Analysis of the composite skin test did not reveal a significant difference between Ranch Hands and Comparisons in the unadjusted analyses of Model 1 (Table 19-4(a): $p>0.11$ for all unadjusted analyses). Overall, the adjusted analysis did not display a significant association between Ranch Hands and Comparisons; however, stratifying by occupation revealed a marginally significant difference between Ranch Hand and Comparison officers (Table 19-4(b): $p=0.131$ and $p=0.084$, Adj. $RR=1.87$ respectively). The covariates age, race, and current cigarette smoking were retained in the final adjusted model.

Model 2 did not display a significant association between initial dioxin and the composite skin test diagnosis (Table 19-4(c,d): $p>0.16$ for both the unadjusted and adjusted

Table 19-4.
Analysis of Composite Skin Test Diagnosis

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Percent Possibly Abnormal**	**Est. Relative Risk (95% C.I.)**	**p-Value**
All	***Ranch Hand***	***919***	***4.2***	***1.46 (0.92,2.31)***	***0.136***
	Comparison	***1,220***	***3.0***		
Officer	Ranch Hand	354	5.4	1.87 (0.92,3.78)	0.113
	Comparison	475	2.9		
Enlisted Flyer	Ranch Hand	158	3.8	1.22 (0.39,3.87)	0.961
	Comparison	192	3.1		
Enlisted Groundcrew	Ranch Hand	407	3.4	1.20 (0.58,2.48)	0.769
	Comparison	553	2.9		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	**Adj. Relative Risk (95% C.I.)**	**p-Value**	**Covariate Remarks[a]**
All	***1.43 (0.90,2.28)***	***0.131***	AGE (p=0.001) RACE (p=0.005) CSMOK (p=0.026)
Officer	1.87 (0.92,3.80)	0.084	
Enlisted Flyer	1.14 (0.36,3.62)	0.828	
Enlisted Groundcrew	1.18 (0.57,2.46)	0.659	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-4. (Continued)
Analysis of Composite Skin Test Diagnosis

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Possibly Abnormal	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	169	5.3	0.77 (0.49,1.22)	0.240
Medium	170	1.8		
High	167	1.8		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)[c]			
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
499	0.74 (0.47,1.16)	0.163	RACE (p=0.064) ALC (p=0.024)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-4. (Continued)
Analysis of Composite Skin Test Diagnosis

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	**n**	**Percent Possibly Abnormal**	**Est. Relative Risk (95% C.I.)[ab]**	**p-Value**
Comparison	1,019	2.9		
Background RH	358	6.1	1.93 (1.09,3.43)	0.024
Low RH	252	4.0	1.37 (0.65,2.85)	0.407
High RH	254	2.0	0.71 (0.27,1.87)	0.491
Low plus High RH	506	3.0	1.05 (0.55,1.98)	0.886

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	**n**	**Adj. Relative Risk (95% C.I.)[ac]**	**p-Value**	**Covariate Remarks**
Comparison	1,004			DXCAT*ALC (p=0.022) AGE (p=0.024) RACE (p=0.008) CSMOK (p=0.120)
Background RH	356	1.80 (1.01,3.20)**	0.047**	
Low RH	249	1.41 (0.67,2.97)**	0.363**	
High RH	250	0.78 (0.30,2.06)**	0.435**	
Low plus High RH	499	1.11 (0.59,2.12)**	0.744**	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

** Categorized dioxin-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-1 for further analysis of this interaction.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.
DXCAT = Categorized Dioxin.

Table 19-4. (Continued)
Analysis of Composite Skin Test Diagnosis

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Possibly Abnormal/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	6.0 (283)	5.2 (289)	1.7 (292)	0.72 (0.56,0.93)	0.008
5	6.3 (288)	5.2 (286)	1.4 (290)	0.78 (0.65,0.94)	0.012
6[c]	6.3 (287)	5.2 (286)	1.4 (290)	0.78 (0.63,0.95)	0.014

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	845	0.76 (0.59,0.98)	0.029	AGE (p=0.085) RACE (p=0.048) DRKYR (p=0.147) CSMOK (p=0.119)
5	864	0.82 (0.68,0.99)	0.037	AGE (p=0.044) RACE (p=0.050) CSMOK (p=0.084)
6[d]	863	0.80 (0.64,0.99)**	0.047**	CURR*OCC (p=0.039) AGE (p=0.040) RACE (p=0.030) CSMOK (p=0.114)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

** Log_2 (current dioxin + 1)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-1 for further analysis of this interaction.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.
CURR = Log_2 (current dioxin + 1).

analyses). Race and current alcohol use were included in the final adjusted model. In Model 3, the unadjusted analysis exhibited a significantly higher percentage of abnormal skin tests in background Ranch Hands (6.1%) than in Comparisons (2.9%) (Table 19-4(e): p=0.024, Est. RR=1.93). Adjusting for covariates in Model 3 revealed a significant categorized dioxin-by-current alcohol use interaction (Table 19-4(f): p=0.022). Stratified results of the interaction between current alcohol use and categorized dioxin are presented in Appendix Table O-2-1. Removal of the interaction revealed a significant difference between background Ranch Hands and Comparisons (Table 19-4(f): p=0.047, Adj. RR=1.80). Age, race, and current cigarette smoking also were in the final adjusted model.

The unadjusted analyses of Models 4 through 6 showed significant inverse associations between the composite skin test diagnosis and current dioxin (Table 19-4(g): p=0.008, Est. RR=0.72; p=0.012, Est. RR=0.78; and p=0.014, Est. RR=0.78 for Models 4, 5, and 6 respectively). The adjusted analysis for composite skin test also revealed significant inverse relationships with current dioxin in Models 4 and 5 (Table 19-4(h): p=0.029, Adj. RR=0.76 and p=0.037, Adj. RR=0.82). The final adjusted model of Model 4 contained the covariates age, race, lifetime alcohol history, and current cigarette smoking. Model 5 contained age, race, and current cigarette smoking in the final adjusted model. Adjusting for covariates in Model 6 revealed a significant current dioxin-by-occupation interaction (Table 19-4(h): p=0.039). In Model 6, the covariates age, race, and current cigarette smoking also were retained in the final adjusted model. Removal of the interaction from the model revealed a significant inverse association between current dioxin and composite skin test diagnosis (Table 19-4(h): p=0.047, Adj. RR=0.80). Further analyses of the current dioxin-by-occupation interaction stratified by occupation were performed. These stratified results are presented in Appendix Table O-2-1. When occupation was removed from the Model 6 final adjusted model, the association between current dioxin and composite skin test diagnosis became marginally significant (Appendix Table O-3-1(a): p=0.062).

Laboratory Examination Variables

CD3 Cells

The unadjusted Model 1 analysis discovered a significant difference in mean CD3 cell count between Ranch Hand and Comparison officers (Table 19-5(a): p=0.039). Ranch Hand officers had a higher mean CD3 cell count (1,474.0 cells/mm^3) than Comparison officers (1,326.5 cells/mm^3). After adjusting for current cigarette smoking, the Model 1 analyses were nonsignificant (Table 19-5(b): p>0.13).

The unadjusted analysis of Models 2 and 3 did not find any significant associations between CD3 cell count and initial dioxin (Table 19-5(c,e): p>0.29). The adjusted Model 2 analysis revealed a significant interaction between initial dioxin and occupation (Table 19-5(d): p=0.032). Stratified analyses of this interaction are presented in Appendix Table O-2-2. Age, current cigarette smoking, and lifetime alcohol use also were included in the final adjusted Model 2 analysis. After removing the interaction with initial dioxin from the adjusted model, the results were nonsignificant (Table 19-5(d): p=0.760). The adjusted Model 3 analysis also detected significant categorized dioxin-by-age and categorized dioxin-by-occupation interactions (Table 19-5(f): p=0.015 and p=0.012). For further investigation

Table 19-5.
Analysis of CD3 Cells (cells/mm^3)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Mean[ab]**	**Difference of Means (95% C.I.)[c]**	**p-Value[d]**
All	*Ranch Hand*	*367*	*1,481.0*	*23.0 --*	*0.584*
	Comparison	*482*	*1,458.0*		
Officer	Ranch Hand	154	1,474.0	147.5 --	0.039
	Comparison	176	1,326.5		
Enlisted Flyer	Ranch Hand	66	1,436.6	-109.3 --	0.450
	Comparison	83	1,545.9		
Enlisted Groundcrew	Ranch Hand	147	1,542.8	57.8 --	0.390
	Comparison	223	1,485.0		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	**Group**	**n**	**Adj. Mean[ae]**	**Difference of Adj. Means (95% C.I.)[c]**	**p-Value[d]**	**Covariate Remarks[f]**
All	*Ranch Hand*	*367*	*1,483.4*	*24.4 --*	0.544	CSMOK ($p<0.001$)
	Comparison	*481*	*1,459.0*			
Officer	Ranch Hand	154	1,481.5	93.2 --	0.134	
	Comparison	176	1,388.3			
Enlisted Flyer	Ranch Hand	66	1,410.0	-122.3 --	0.201	
	Comparison	83	1,532.3			
Enlisted Groundcrew	Ranch Hand	147	1,523.1	31.6 --	0.619	
	Comparison	222	1,491.5			

[a] Transformed from the natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[c] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

[d] P-values based on difference of means on natural logarithm scale.

[e] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

[f] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-5. (Continued)
Analysis of CD3 Cells (cells/mm^3)

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED						
Initial Dioxin Category Summary Statistics				Analysis Results for Log_2 (Initial Dioxin)[b]		
Initial Dioxin	n	Mean[a]	Adj. Mean[ab]	R^2	Slope (Std. Error)[c]	p-Value
Low	64	1,390.4	1,414.3	0.476	0.013 (0.026)	0.627
Medium	67	1,538.7	1,568.9			
High	72	1,534.9	1,506.6			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	64	1,528.7**	0.558	-0.010 (0.031)**	0.760**	INIT*OCC (p=0.032) AGE (p=0.095) CSMOK (p=0.006) DRKYR (p=0.092)
Medium	65	1,592.0**				
High	71	1,520.2**				

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

[c] Slope and standard error based on natural logarithm of CD3 cells versus $\log_2$ (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

** Log_2 (initial dioxin)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-2 for further analysis of this interaction.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.
INIT = Log_2 (initial dioxin).

Table 19-5. (Continued)
Analysis of CD3 Cells (cells/mm^3)

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED					
Dioxin Category	n	Mean[a]	Adj. Mean[ab]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]
Comparison	404	1,440.7	1,440.3		
Background RH	141	1,494.0	1,499.7	59.4 --	0.321
Low RH	95	1,384.6	1,387.1	-53.2 --	0.428
High RH	108	1,515.5	1,509.0	68.7 --	0.298
Low plus High RH	203	1,452.8	1,450.7	10.4 --	0.841

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED					
Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	400	1,445.2**			DXCAT*AGE (p=0.015) DXCAT*OCC (p=0.012) CSMOK (p<0.001) ALC (p=0.064)
Background RH	140	1,507.9**	62.7 --**	0.301**	
Low RH	95	1,419.6**	-25.6 --**	0.700**	
High RH	106	1,492.2**	47.0 --**	0.472**	
Low plus High RH	201	1,457.4**	12.2 --**	0.809**	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

[c] Difference of adjusted means after transformation to original scale; confidence interval on difference of adjusted means not presented because analysis was performed on natural logarithm scale.

[d] P-value is based on difference of means on natural logarithm scale.

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

** Categorized dioxin-by-covariate interactions ($0.01 < p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of these interactions; refer to Appendix Table O-2-2 for further analysis of these interactions.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-5. (Continued)
Analysis of CD3 Cells (cells/mm³)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean[ab]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[c]	Low	Medium	High	R^2	Slope (Std. Error)[d]	p-Value
4	1,470.2 (116)	1,515.4 (107)	1,515.4 (121)	0.296	-0.002 (0.017)	0.896
5	1,487.1 (112)	1,395.5 (116)	1,395.5 (116)	0.296	-0.001 (0.015)	0.967
6[e]	1,450.1 (112)	1,504.7 (116)	1,504.7 (116)	0.300	-0.008 (0.016)	0.629

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean[af]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[c]	Low	Medium	High	R^2	Adj. Slope (Std. Error)[d]	p-Value	Covariate Remarks
4	1,458.1 (115)	1,516.7 (107)	1,446.2 (119)	0.353	-0.000 (0.016)	0.988	CSMOK ($p<0.001$) ALC ($p=0.079$)
5	1,507.5 (111)	1,414.9 (116)	1,506.7 (114)	0.353	0.003 (0.014)	0.855	CSMOK ($p<0.001$) ALC ($p=0.077$)
6[e]	1,503.6 (111)	1,399.3 (116)	1,449.7 (114)	0.366	-0.008 (0.015)	0.616	CSMOK ($p<0.001$) ALC ($p=0.060$) PHYACT ($p=0.145$)

[a] Transformed from natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[c] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[d] Slope and standard error based on natural logarithm of CD3 cells versus log_2 (current dioxin + 1).

[e] Adjusted for log_2 total lipids.

[f] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

of these interactions, stratified analyses are presented in Appendix Table O-2-2. The adjusted Model 3 analysis also accounted for current cigarette smoking and current alcohol use. After removing the interactions from the adjusted model, the Model 3 results were nonsignificant (Table 19-5(f): $p>0.30$).

None of the unadjusted or adjusted analyses of Models 4 through 6 displayed any significant relationships between current dioxin and CD3 cell count (Table 19-5(g,h): $p>0.61$). Current cigarette smoking and current alcohol use were retained in the final adjusted analyses of Models 4 through 6, and Model 6 also included physical activity index.

CD4 Cells

The unadjusted Model 1 analysis of CD4 cell count exhibited a marginally significant difference between Ranch Hand and Comparison officers (Table 19-6(a): $p=0.054$). Ranch Hand officers had a higher mean CD4 cell count (964.5 cells/mm^3) than Comparison officers (873.0 cells/mm^3). After adjusting for age and current cigarette smoking, the Model 1 analysis was nonsignificant (Table 19-6(b): $p>0.20$).

The unadjusted and adjusted Model 2 analysis of CD4 cells as well as the unadjusted Model 3 analysis did not detect any significant associations between dioxin and CD4 cell counts (Table 19-6(c,d,e): $p>0.24$). The final adjusted Model 2 analysis accounted for current cigarette smoking. The Model 3 adjusted analysis revealed significant interactions between categorized dioxin and age and occupation (Table 19-6(f): $p=0.041$ and $p=0.047$). Stratified analyses of these interactions are presented in Appendix Table O-2-3. The adjusted Model 3 analysis also accounted for current cigarette smoking. After removing the interactions with categorized dioxin from the adjusted model, the Model 3 results were nonsignificant (Table 19-6(f): $p>0.33$ for all contrasts).

The unadjusted analyses of Models 4 through 6 did not reveal any significant relationships between CD4 cells and current dioxin (Table 19-6(g,h): $p>0.64$). The final models for Models 4 through 6 were adjusted for current cigarette smoking.

CD5 Cells

The unadjusted Model 1 analysis of CD5 cells detected a significant difference between Ranch Hand and Comparison officers (Table 19-7(a): $p=0.035$). Ranch Hand officers had a higher mean CD5 cell count (1,524.7 cells/mm^3) than Comparison officers (1,366.7 cells/mm^3). The adjusted Model 1 analysis was nonsignificant (Table 19-7(b): $p>0.13$). Current cigarette smoking, current alcohol use, and physical activity index were included in the final adjusted Model 1 analysis.

The Model 2 and 3 unadjusted analyses of CD5 cells were nonsignificant (Table 19-7(c,e): $p>0.20$). The adjusted Model 2 analysis detected a significant interaction between initial dioxin and occupation (Table 19-7(d): $p=0.031$). Stratified analyses were performed for each occupational category and are presented in Appendix Table O-2-4. The final Model 2 analysis also was adjusted for age, current cigarette smoking, and lifetime alcohol history. After removing the interaction from the adjusted model, the Model 2 results

Table 19-6.
Analysis of CD4 Cells (cells/mm^3)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Mean[ab]**	**Difference of Means (95% C.I.)[c]**	**p-Value[d]**
All	*Ranch Hand*	*367*	*953.5*	*15.3 --*	*0.581*
	Comparison	*482*	*938.2*		
Officer	Ranch Hand	154	964.5	91.5 --	0.054
	Comparison	176	873.0		
Enlisted Flyer	Ranch Hand	66	909.3	-83.2 --	0.400
	Comparison	83	992.5		
Enlisted Groundcrew	Ranch Hand	147	998.9	55.0 --	0.217
	Comparison	223	943.9		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	**Group**	**n**	**Adj. Mean[ae]**	**Difference of Adj. Means (95% C.I.)[c]**	**p-Value[d]**	**Covariate Remarks[f]**
All	*Ranch Hand*	*367*	*956.9*	*19.7 --*	0.454	AGE (p=0.040)
	Comparison	*481*	*937.2*			CSMOK (p<0.001)
Officer	Ranch Hand	154	973.8	53.3 --	0.204	
	Comparison	176	920.5			
Enlisted Flyer	Ranch Hand	66	900.8	-75.5 --	0.227	
	Comparison	83	976.3			
Enlisted Groundcrew	Ranch Hand	147	966.3	28.8 --	0.484	
	Comparison	222	937.5			

[a] Transformed from the natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[c] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

[d] P-values based on difference of means on natural logarithm scale.

[e] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

[f] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-6. (Continued)
Analysis of CD4 Cells (cells/mm³)

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED						
Initial Dioxin Category Summary Statistics				Analysis Results for Log_2 (Initial Dioxin)[b]		
Initial Dioxin	n	Mean[a]	Adj. Mean[ab]	R^2	Slope (Std. Error)[c]	p-Value
Low	64	878.0	894.5	0.465	0.010 (0.027)	0.705
Medium	67	993.5	1,014.8			
High	72	959.4	940.1			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	64	929.0	0.518	-0.008 (0.026)	0.770	CSMOK ($p<0.001$)
Medium	67	1,008.8				
High	72	919.3				

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

[c] Slope and standard error based on natural logarithm of CD4 cells versus $\log_2$ (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-6. (Continued)
Analysis of CD4 Cells (cells/mm^3)

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED					
Dioxin Category	n	Mean[a]	Adj. Mean[ab]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]
Comparison	404	922.0	921.8		
Background RH	141	957.4	960.4	38.6 --	0.330
Low RH	95	885.7	889.6	-32.2 --	0.468
High RH	108	977.6	972.5	50.7 --	0.246
Low plus High RH	203	933.4	932.8	11.0 --	0.747

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED					
Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	403	922.5**			DXCAT*AGE (p=0.041)
Background RH	141	960.5**	38.0 --**	0.331**	DXCAT*OCC (p=0.047)
Low RH	95	916.7**	-5.8 --**	0.893**	CSMOK (p<0.001)
High RH	108	962.1**	39.6 --**	0.348**	
Low plus High RH	203	940.6**	18.1 --**	0.583**	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

[c] Difference of adjusted means after transformation to original scale; confidence interval on difference of adjusted means not presented because analysis was performed on natural logarithm scale.

[d] P-value is based on difference of means on natural logarithm scale.

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

** Categorized dioxin-by-covariate interactions ($0.01<p\leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of these interactions; refer to Appendix Table O-2-3 for further analysis of these interactions.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-6. (Continued)
Analysis of CD4 Cells (cells/mm^3)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean[ab]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[c]	Low	Medium	High	R^2	Slope (Std. Error)[d]	p-Value
4	930.0 (116)	944.4 (107)	942.2 (121)	0.269	0.001 (0.017)	0.974
5	970.3 (112)	886.0 (116)	966.7 (116)	0.269	0.003 (0.015)	0.866
6[e]	990.1 (112)	888.2 (116)	951.2 (116)	0.276	-0.007 (0.016)	0.647

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean[af]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[c]	Low	Medium	High	R^2	Adj. Slope (Std. Error)[d]	p-Value	Covariate Remarks
4	926.2 (116)	961.9 (107)	936.6 (121)	0.333	0.001 (0.017)	0.972	CSMOK ($p<0.001$)
5	968.4 (112)	897.4 (116)	962.7 (116)	0.333	0.004 (0.014)	0.790	CSMOK ($p<0.001$)
6[e]	987.7 (112)	899.5 (116)	947.7 (116)	0.340	-0.006 (0.016)	0.719	CSMOK ($p<0.001$)

[a] Transformed from natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[c] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[d] Slope and standard error based on natural logarithm of CD4 cells versus log_2 (current dioxin + 1).

[e] Adjusted for log_2 total lipids.

[f] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 19-7.
Analysis of CD5 Cells (cells/mm^3)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Mean[ab]**	**Difference of Means (95% C.I.)[c]**	**p-Value[d]**
All	*Ranch Hand*	*367*	*1,530.7*	*29.5 --*	*0.497*
	Comparison	*482*	*1,501.2*		
Officer	Ranch Hand	154	1,524.7	158.0 --	0.035
	Comparison	176	1,366.7		
Enlisted Flyer	Ranch Hand	66	1,480.7	105.8 --	0.495
	Comparison	83	1,586.5		
Enlisted Groundcrew	Ranch Hand	147	1,595.9	69.3 --	0.310
	Comparison	223	1,526.6		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	**Group**	**n**	**Adj. Mean[ae]**	**Difference of Adj. Means (95% C.I.)[c]**	**p-Value[d]**	**Covariate Remarks[f]**
All	*Ranch Hand*	*364*	*1,513.7*	*36.6 --*	0.377	AGE (p=0.114)
	Comparison	*477*	*1,477.1*			CSMOK (p<0.001)
Officer	Ranch Hand	154	1,528.9	97.3 --	0.134	ALC (p=0.132)
	Comparison	174	1,431.6			PHYACT (p=0.103)
Enlisted Flyer	Ranch Hand	64	1,437.1	-122.8 --	0.217	
	Comparison	83	1,559.9			
Enlisted Groundcrew	Ranch Hand	146	1,538.1	47.9 --	0.460	
	Comparison	220	1,490.2			

[a] Transformed from the natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[c] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

[d] P-values based on difference of means on natural logarithm scale.

[e] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

[f] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-7. (Continued)
Analysis of CD5 Cells (cells/mm^3)

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED						
Initial Dioxin Category Summary Statistics				Analysis Results for Log_2 (Initial Dioxin)[b]		
Initial Dioxin	n	Mean[a]	Adj. Mean[ab]	R^2	Slope (Std. Error)[c]	p-Value
Low	64	1,430.4	1,458.8	0.479	0.016 (0.027)	0.545
Medium	67	1,595.4	1,631.7			
High	72	1,595.5	1,561.8			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	64	1,582.7**	0.558	-0.008 (0.032)**	0.809**	INIT*OCC (p=0.031)
Medium	65	1,653.8**				AGE (p=0.072)
						CSMOK (p=0.013)
High	71	1,569.7**				DRKYR (p=0.090)

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

[c] Slope and standard error based on natural logarithm of CD5 Cells versus $\log_2$ (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

** Log_2 (initial dioxin)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-4 for further analysis of this interaction.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-7. (Continued)
Analysis of CD5 Cells (cells/mm³)

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED					
Dioxin Category	n	Mean[a]	Adj. Mean[ab]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]
Comparison	404	1,482.2	1,481.8		
Background RH	141	1,533.3	1,539.7	57.9 --	0.348
Low RH	95	1,422.2	1,425.1	-56.7 --	0.412
High RH	108	1,576.1	1,568.7	86.9 --	0.204
Low plus High RH	203	1,502.1	1,499.8	18.0 --	0.737

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED					
Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	400	1,486.5**			DXCAT*AGE (p=0.012) DXCAT*OCC (p=0.011) CSMOK (p<0.001) ALC (p=0.038)
Background RH	140	1,548.0**	61.5 --**	0.326**	
Low RH	95	1,464.2**	-22.3 --**	0.745**	
High RH	106	1,552.3**	65.8 --**	0.333**	
Low plus High RH	201	1,510.0**	23.5 --**	0.655**	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

[c] Difference of adjusted means after transformation to original scale; confidence interval on difference of adjusted means not presented because analysis was performed on natural logarithm scale.

[d] P-value is based on difference of means on natural logarithm scale.

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

** Categorized dioxin-by-covariate interactions ($0.01 < p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of these interactions; refer to Appendix Table O-2-4 for further analysis of these interactions.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-7. (Continued)

Analysis of CD5 Cells (cells/mm³)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[b]	Low	Medium	High	R^2	Slope (Std. Error)[c]	p-Value
4	1,505.4 (116)	1,524.4 (107)	1,510.0 (121)	0.282	0.003 (0.017)	0.865
5	1,553.6 (112)	1,425.3 (116)	1,572.4 (116)	0.282	0.004 (0.015)	0.802
6[d]	1,574.5 (112)	1,427.6 (116)	1,555.7 (116)	0.285	-0.003 (0.016)	0.838

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[b]	Low	Medium	High	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
4	1,470.1 (115)	1,532.4 (107)	1,465.8 (119)	0.346	0.002 (0.016)	0.919	CSMOK (p<0.001) ALC (p=0.041) PHYACT (p=0.145)
5	1,520.5 (111)	1,427.1 (116)	1,539.0 (114)	0.346	0.005 (0.014)	0.750	CSMOK (p<0.001) ALC (p=0.039) PHYACT (p=0.149)
6[e]	1,540.8 (111)	1,428.3 (116)	1,517.4 (114)	0.350	-0.003 (0.015)	0.836	CSMOK (p<0.001) ALC (p=0.037) PHYACT (p=0.119)

[a] Transformed from natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[c] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[d] Slope and standard error based on natural logarithm of CD5 cells versus log_2 (current dioxin + 1).

[e] Adjusted for log_2 total lipids.

[f] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

were nonsignificant (Table 19-7(d): $p=0.351$). The adjusted Model 3 analysis of CD5 cells revealed significant interactions between categorized dioxin and age and occupation (Table 19-7(f): $p=0.012$ and $p=0.011$, respectively). For further investigation of these interactions, stratified analyses are presented in Appendix Table O-2-4. The final Model 3 analysis also was adjusted for current cigarette smoking and current alcohol use. The adjusted model after removal of the two interactions with categorized dioxin did not exhibit any significant relationships between categorized dioxin and CD5 cell count (Table 19-7(f): $p>0.32$).

The unadjusted and adjusted analyses of Models 4 through 6 did not detect any significant relationships between current dioxin and CD5 cells (Table 19-7(g,h): $p>0.75$). Current cigarette smoking, current alcohol use, and physical activity index were retained in the final adjusted analyses of Models 4 through 6.

CD8 Cells

Both the unadjusted and adjusted Model 1 analyses of CD8 cells revealed a marginally significant difference in mean CD8 cell counts between Ranch and Comparison enlisted flyers (Table 19-8(a,b): $p=0.053$ unadjusted; $p=0.055$ adjusted). Ranch Hand enlisted flyers had a lower mean CD8 cell count (603.8 and 597.5 cells/mm^3 unadjusted and adjusted) than Comparison enlisted flyers (700.9 and 691.9 cells/mm^3 unadjusted and adjusted). The adjusted Model 1 analyses accounted for current cigarette smoking.

The unadjusted Model 2 and 3 analyses of CD8 cell counts were nonsignificant (Table 19-9(c,e): $p>0.44$). The adjusted Model 2 analysis displayed a highly significant interaction between initial dioxin and occupation, and results stratified by occupation are presented in Appendix Table O-2-5. Officers displayed a significant positive association between CD8 cell counts and initial dioxin (Appendix Table O-2-5(a): $p=0.007$, Adj. Slope=0.493). The adjusted Model 2 analysis also accounted for current cigarette smoking and current alcohol use. The adjusted Model 3 analysis also detected significant categorized dioxin-by-age and categorized dioxin-by-occupation interactions. Stratified analyses of these interactions are presented in Appendix Table O-2-5. The final Model 3 analysis also was adjusted for current cigarette smoking and current alcohol use. After removing the interactions from the adjusted model, the results were nonsignificant (Table 19-8(f): $p>0.40$).

The unadjusted analyses of Models 4 through 6 did not show any significant relationships between current dioxin and CD8 cell counts (Table 19-8(g): $p>0.59$). The adjusted Model 4 analysis detected a significant interaction between current dioxin and occupation (Table 19-8(h): $p=0.050$). For further investigation of this interaction, stratified analyses are presented in Appendix Table O-2-5. The final adjusted Model 4 analysis also was adjusted for current cigarette smoking and current alcohol use. After removal of the interaction with current dioxin, the adjusted Model 4 analysis was nonsignificant (Table 19-8(h): $p=0.742$). Similarly, the adjusted analyses of Models 5 and 6 did not exhibit any significant associations between current dioxin and CD8 cell counts (Table 19-8(h): $p>0.66$). Models 5 and 6 were adjusted for current cigarette smoking and current alcohol use.

Table 19-8.
Analysis of CD8 Cells (cells/mm^3)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Mean[a]**	**Difference of Means (95% C.I.)[b]**	**p-Value[c]**
All	***Ranch Hand***	***367***	***628.3***	***-4.7 --***	***0.817***
	Comparison	***482***	***633.0***		
Officer	Ranch Hand	154	617.7	24.4 --	0.470
	Comparison	176	593.3		
Enlisted Flyer	Ranch Hand	66	603.8	-97.1 --	0.053
	Comparison	83	700.9		
Enlisted Groundcrew	Ranch Hand	147	651.1	9.7 --	0.746
	Comparison	223	641.4		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	**Group**	**n**	**Adj. Mean[a]**	**Difference of Adj. Means (95% C.I.)[b]**	**p-Value[c]**	**Covariate Remarks[d]**
All	***Ranch Hand***	***367***	***628.8***	***-3.8 --***	0.851	CSMOK ($p<0.001$)
	Comparison	***481***	***632.6***			
Officer	Ranch Hand	154	626.2	23.5 --	0.453	
	Comparison	176	602.7			
Enlisted Flyer	Ranch Hand	66	597.5	-94.4 --	0.055	
	Comparison	83	691.9			
Enlisted Groundcrew	Ranch Hand	147	646.0	10.3 --	0.745	
	Comparison	222	635.7			

[a] Transformed from the natural logarithm scale.

[b] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

[c] P-values based on difference of means on natural logarithm scale.

[d] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-8. (Continued)
Analysis of CD8 Cells (cells/mm³)

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED						
Initial Dioxin Category Summary Statistics				Analysis Results for Log_2 (Initial Dioxin)[b]		
Initial Dioxin	n	Mean[a]	Adj. Mean[ab]	R^2	Slope (Std. Error)[c]	p-Value
Low	64	601.4	601.6	0.001	0.008 (0.028)	0.763
Medium	67	615.6	615.8			
High	72	631.2	630.8			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	64	****	0.136	****	****	INIT*OCC (p=0.001) CSMOK (p=0.009) ALC (p=0.016)
Medium	66	****				
High	71	****				

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Slope and standard error based on natural logarithm of CD8 Cells versus $\log_2$ (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

**** Log_2 (initial dioxin)-by-covariate interaction ($p \leq 0.01$); adjusted mean, adjusted slope, standard error, and p-value not presented; refer to Appendix Table O-2-5 for further analysis of this interaction.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-8. (Continued)
Analysis of CD8 Cells (cells/mm³)

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED					
Dioxin Category	n	Mean[a]	Adj. Mean[ab]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]
Comparison	404	629.2	629.0		
Background RH	141	636.7	639.1	10.1 --	0.734
Low RH	95	606.3	603.8	-25.2 --	0.447
High RH	108	625.6	625.6	-3.4 --	0.916
Low plus High RH	203	616.5	615.3	-13.7 --	0.588

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED					
Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	400	633.6**			DXCAT*AGE (p=0.020) DXCAT*OCC (p=0.001) CSMOK (p<0.001) ALC (p=0.033)
Background RH	140	645.3**	11.7 --**	0.705**	
Low RH	95	606.3**	-27.3 --**	0.413**	
High RH	106	618.4**	-15.2 --**	0.645**	
Low plus High RH	201	612.7**	-20.9 --**	0.409**	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Difference of adjusted means after transformation to original scale; confidence interval on difference of adjusted means not presented because analysis was performed on natural logarithm scale.

[d] P-value is based on difference of means on natural logarithm scale.

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

** Categorized dioxin-by-covariate interactions ($p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of these interactions; refer to Appendix Table O-2-5 for further analysis of these interactions.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-8. (Continued)
Analysis of CD8 Cells (cells/mm^3)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[b]	Low	Medium	High	R^2	Slope (Std. Error)[c]	p-Value
4	628.4 (116)	652.2 (107)	598.0 (121)	0.001	-0.009 (0.019)	0.639
5	625.5 (112)	629.7 (116)	619.1 (116)	0.001	-0.009 (0.016)	0.592
6[d]	624.9 (112)	629.6 (116)	619.7 (116)	0.001	-0.009 (0.018)	0.602

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[b]	Low	Medium	High	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
4	620.9** (115)	657.5** (107)	574.7** (119)	0.068	-0.007 (0.022)**	0.742**	CURR*OCC (p=0.050) CSMOK (p<0.001) ALC (p=0.078)
5	619.8 (111)	634.5 (116)	612.9 (114)	0.048	-0.006 (0.016)	0.728	CSMOK (p<0.001) ALC (p=0.142)
6[e]	621.3 (111)	634.6 (116)	611.3 (114)	0.048	-0.008 (0.017)	0.663	CSMOK (p<0.001) ALC (p=0.137)

[a] Transformed from natural logarithm scale.

[b] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[c] Slope and standard error based on natural logarithm of CD8 cells versus log_2 (current dioxin + 1).

[d] Adjusted for log_2 total lipids.

[e] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

** Log_2 (current dioxin + 1)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-5 for further analysis of this interaction.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

CD14 Cells

The Model 1 unadjusted analyses of CD14 cell counts were nonsignificant (Table 19-9(a): $p>0.14$). The adjusted analyses displayed a significant interaction between group and occupation (Table 19-9(b): $p=0.044$). Analyses stratified by occupational category revealed a significant difference in mean CD8 cell counts between Ranch Hand and Comparison enlisted flyers (Table 19-9(b): $p=0.021$). Ranch Hand enlisted flyers had a lower mean CD14 cell count (449.8 cells.mm^3) than Comparison enlisted flyers (505.9 cells/mm^3).

The unadjusted and adjusted Model 2 analyses of CD14 cell counts did not detect a significant relationship with initial dioxin (Table 19-9(c,d): $p>0.24$). Model 2 was adjusted for current cigarette smoking and lifetime alcohol history. The Model 3 unadjusted analysis of CD14 cell counts detected a significant difference between Comparisons and Ranch Hands in the low initial dioxin category and a marginally significant difference between Comparisons and Ranch Hands in the low plus high category (Table 19-9(e): $p=0.033$ and $p=0.092$ respectively). Comparisons had a higher mean CD14 cell count (523.5 cells/mm^3) than Ranch Hands in the low initial dioxin category (483.7 cells/mm^3) and in the low plus high category (500.1 cells/mm^3). The adjusted Model 3 analysis detected a highly significant interaction between categorized dioxin and age (Table 19-9(f): $p=0.002$). Stratified analyses of this interaction are presented in Appendix Table O-2-6. Older Ranch Hands in the low, high, and low plus high dioxin categories had significantly or marginally significantly lower mean CD14 cell counts than Comparisons (Appendix Table O-2-6(b): $p=0.008$, $p=0.061$, and $p=0.003$ respectively). The adjusted Model 3 analysis also accounted for occupation, race, current cigarette smoking, and physical activity index.

None of the unadjusted and adjusted analyses of Models 4 through 6 revealed any significant associations between CD14 cell counts and current dioxin (Table 19-9(g,h): $p>0.38$). Each of Models 4 through 6 were adjusted for age, occupation, race, and current cigarette smoking.

CD16+56 Cells

The unadjusted analysis of Model 1 revealed a marginally significant difference in mean CD16+56 cell count between enlisted flyer Ranch Hands and Comparisons (Table 19-10(a): $p=0.097$). Ranch Hand enlisted flyers had a lower mean CD16+56 cell count (221.5 cells/mm^3) than Comparison enlisted flyers (278.0 cells/mm^3). However, after adjusting for age and current cigarette smoking, the Model 1 analysis of CD16+56 cell counts was nonsignificant (Table 19-10(b): $p>0.11$).

The unadjusted Model 2 and 3 analyses of CD16+56 cells were nonsignificant (Table 19-10(c,e): $p>0.14$). The adjusted Model 2 analysis detected significant interactions between initial dioxin and occupation and physical activity index (Table 19-10(d): $p=0.003$ and $p=0.039$ respectively). Stratified analyses of these interactions are presented in Appendix Table O-2-7. Current cigarette smoking also was included in the adjusted Model 2 analysis. After removal of the interactions from the final model, the Model 2 analysis was nonsignificant (Table 19-10(d): $p=0.724$). Similar to the Model 2 analysis, the adjusted

Table 19-9.
Analysis of CD14 Cells (cells/mm^3)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Mean[ab]**	**Difference of Means (95% C.I.)[c]**	**p-Value[d]**
All	***Ranch Hand***	***367***	***520.8***	***-2.5 --***	***0.834***
	Comparison	***482***	***523.3***		
Officer	Ranch Hand	154	524.3	30.3 --	0.146
	Comparison	176	494.0		
Enlisted Flyer	Ranch Hand	66	517.5	-20.5 --	0.615
	Comparison	83	538.0		
Enlisted Groundcrew	Ranch Hand	147	524.8	-10.9 --	0.591
	Comparison	223	535.7		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	**Group**	**n**	**Adj. Mean[ae]**	**Difference of Adj. Means (95% C.I.)[c]**	**p-Value[d]**	**Covariate Remarks[f]**
All	***Ranch Hand***	***367***	***484.7*****	***-2.8 --*****	0.784**	GROUP*OCC (p=0.044)
	Comparison	***481***	***487.5*****			AGE (p<0.001)
Officer	Ranch Hand	154	478.1	16.5 --	0.300	RACE (p=0.001)
	Comparison	176	461.6			CSMOK (p<0.001)
Enlisted Flyer	Ranch Hand	66	449.8	-56.1 --	0.021	
	Comparison	83	505.9			
Enlisted Groundcrew	Ranch Hand	147	510.7	1.1 --	0.952	
	Comparison	222	509.6			

[a] Transformed from the natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[c] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

[d] P-values based on difference of means on natural logarithm scale.

[e] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

[f] Covariates and associated p-values correspond to final model based on all participants with available data.

** Group-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-6 for further analysis of this interaction.

Table 19-9. (Continued)
Analysis of CD14 Cells (cells/mm^3)

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED						
Initial Dioxin Category Summary Statistics				Analysis Results for Log_2 (Initial Dioxin)[b]		
Initial Dioxin	n	Mean[a]	Adj. Mean[ab]	R^2	Slope (Std. Error)[c]	p-Value
Low	64	482.5	488.4	0.394	0.028 (0.024)	0.249
Medium	67	489.5	496.4			
High	72	536.3	529.6			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	64	515.9	0.471	0.009 (0.024)	0.714	CSMOK ($p<0.001$) DRKYR ($p=0.050$)
Medium	65	501.1				
High	71	525.0				

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

[c] Slope and standard error based on natural logarithm of CD14 cells versus $\log_2$ (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-9. (Continued)
Analysis of CD14 Cells (cells/mm³)

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED					
Dioxin Category	n	Mean[a]	Adj. Mean[ab]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]
Comparison	404	525.7	523.5		
Background RH	141	530.6	535.1	11.6 --	0.581
Low RH	95	484.9	483.7	-39.8 --	0.033
High RH	108	518.1	515.0	-8.5 --	0.586
Low plus High RH	203	502.3	500.1	-23.4 --	0.092

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED					
Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	403	****			DXCAT*AGE (p=0.002) OCC (p=0.083) RACE (p=0.005) CSMOK (p<0.001) PHYACT (p=0.147)
Background RH	141	****	****	****	
Low RH	95	****	****	****	
High RH	108	****	****	****	
Low plus High RH	203	****	****	****	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

[c] Difference of adjusted means after transformation to original scale; confidence interval on difference of adjusted means not presented because analysis was performed on natural logarithm scale.

[d] P-value is based on difference of means on natural logarithm scale.

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

**** Categorized dioxin-by-covariate interaction ($p \leq 0.01$); adjusted mean, difference of adjusted means, and p-value not presented; refer to Appendix Table O-2-6 for further analysis of this interaction.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-9. (Continued)
Analysis of CD14 Cells (cells/mm^3)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean[ab]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[c]	Low	Medium	High	R^2	Slope (Std. Error)[d]	p-Value
4	525.8 (116)	490.6 (107)	500.7 (121)	0.241	-0.004 (0.014)	0.767
5	525.3 (112)	477.8 (116)	517.5 (116)	0.240	0.000 (0.012)	0.985
6[e]	537.9 (112)	479.2 (116)	507.8 (116)	0.256	-0.012 (0.013)	0.383

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean[af]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[c]	Low	Medium	High	R^2	Adj. Slope (Std. Error)[d]	p-Value	Covariate Remarks
4	474.1 (116)	443.7 (107)	439.4 (121)	0.345	-0.007 (0.016)	0.650	AGE ($p=0.016$) OCC ($p=0.059$) RACE ($p=0.005$) CSMOK ($p<0.001$)
5	475.5 (112)	430.2 (116)	464.5 (116)	0.345	0.000 (0.014)	0.992	AGE ($p=0.016$) OCC ($p=0.075$) RACE ($p=0.006$) CSMOK ($p<0.001$)
6[e]	489.9 (112)	435.1 (116)	460.1 (116)	0.354	-0.011 (0.015)	0.461	AGE ($p=0.023$) OCC ($p=0.073$) RACE ($p=0.010$) CSMOK ($p<0.001$)

[a] Transformed from natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[c] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[d] Slope and standard error based on natural logarithm of CD14 cells versus log_2 (current dioxin + 1).

[e] Adjusted for log_2 total lipids.

[f] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 19-10.
Analysis of CD16 + 56 Cells (cells/mm^3)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	Group	n	Mean[ab]	Difference of Means (95% C.I.)[c]	p-Value[d]
All	***Ranch Hand***	***367***	***255.0***	***-11.6 --***	***0.253***
	Comparison	***482***	***266.6***		
Officer	Ranch Hand	154	268.4	16.6 --	0.337
	Comparison	176	251.8		
Enlisted Flyer	Ranch Hand	66	221.5	-56.5 --	0.097
	Comparison	83	278.0		
Enlisted Groundcrew	Ranch Hand	147	258.6	-10.3 --	0.541
	Comparison	223	268.9		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	Group	n	Adj. Mean[ae]	Difference of Adj. Means (95% C.I.)[c]	p-Value[d]	Covariate Remarks[f]
All	***Ranch Hand***	***367***	***254.0***	***-13.8 --***	0.171	AGE (p=0.019)
	Comparison	***481***	***267.8***			CSMOK (p=0.004)
Officer	Ranch Hand	154	256.8	3.3 --	0.832	
	Comparison	176	253.5			
Enlisted Flyer	Ranch Hand	66	235.5	-36.8 --	0.115	
	Comparison	83	272.3			
Enlisted Groundcrew	Ranch Hand	147	260.0	-19.1 --	0.236	
	Comparison	222	279.1			

[a] Transformed from the natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[c] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

[d] P-values based on difference of means on natural logarithm scale.

[e] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

[f] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-10. (Continued)
Analysis of CD16 + 56 Cells (cells/mm^3)

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED						
Initial Dioxin Category Summary Statistics				Analysis Results for Log_2 (Initial Dioxin)[b]		
Initial Dioxin	n	Mean[a]	Adj. Mean[ab]	R^2	Slope (Std. Error)[c]	p-Value
Low	64	255.2	257.6	0.408	-0.007 (0.041)	0.870
Medium	67	241.0	243.6			
High	72	253.4	251.2			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	64	239.5**	0.506	0.015 (0.049)**	0.752**	INIT*OCC (p=0.003) INIT*PHYACT (p=0.039) CSMOK (p=0.053)
Medium	67	238.9**				
High	72	250.1**				

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

[c] Slope and standard error based on natural logarithm of CD16 + 56 cells versus log_2 (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

** Log_2 (initial dioxin)-by-covariate interactions ($p \leq 0.05$); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of these interactions; refer to Appendix Table O-2-7 for further analysis of these interactions.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-10. (Continued)
Analysis of CD16 + 56 Cells (cells/mm^3)

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED

Dioxin Category	n	Mean[a]	Adj. Mean[ab]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]
Comparison	404	261.4	261.4		
Background RH	141	254.8	254.8	-6.6 --	0.647
Low RH	95	240.9	241.7	-19.7 --	0.232
High RH	108	244.9	244.4	-17.0 --	0.277
Low plus High RH	203	243.0	243.2	-18.2 --	0.143

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED

Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	399	248.0**			DXCAT*OCC (p=0.048) DXCAT*DRKYR (p=0.026)
Background RH	139	242.0**	-6.0 --**	0.678**	DXCAT*PHYACT (p=0.038)
Low RH	94	219.3**	-28.7 --**	0.063**	AGE (p<0.001)
High RH	106	236.8**	-11.2 --**	0.465**	RACE (p=0.102) CSMOK (p=0.004)
Low plus High RH	200	228.4**	-19.6 --**	0.097**	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

[c] Difference of adjusted means after transformation to original scale; confidence interval on difference of adjusted means not presented because analysis was performed on natural logarithm scale.

[d] P-value is based on difference of means on natural logarithm scale.

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

** Categorized dioxin-by-covariate interactions ($0.01 < p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of these interactions; refer to Appendix Table O-2-7 for further analysis of these interactions.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-10. (Continued)
Analysis of CD16 + 56 Cells (cells/mm³)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean[ab]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[c]	Low	Medium	High	R^2	Slope (Std. Error)[d]	p-Value
4	244.3 (116)	263.8 (107)	235.1 (121)	0.241	-0.007 (0.024)	0.766
5	250.4 (112)	245.1 (116)	246.5 (116)	0.241	-0.009 (0.020)	0.669
6[e]	248.5 (112)	244.9 (116)	248.0 (116)	0.241	-0.006 (0.022)	0.793

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean[af]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[c]	Low	Medium	High	R^2	Adj. Slope (Std. Error)[d]	p-Value	Covariate Remarks
4	243.3 (116)	255.9 (107)	241.6 (121)	0.258	0.004 (0.024)	0.869	AGE (p=0.086) CSMOK (p=0.140)
5	249.2 (112)	236.3 (116)	255.5 (116)	0.257	-0.001 (0.021)	0.967	AGE (p=0.094) CSMOK (p=0.138)
6[e]	246.9 (112)	235.9 (116)	257.7 (116)	0.258	0.003 (0.023)	0.882	AGE (p=0.088) CSMOK (p=0.143)

[a] Transformed from natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[c] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[d] Slope and standard error based on natural logarithm of CD16 + 56 cells versus log_2 (current dioxin + 1).

[e] Adjusted for log_2 total lipids.

[f] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Model 3 analysis detected significant interactions between categorized dioxin and three covariates: occupation, lifetime alcohol history, and the physical activity index (Table 19-10(f): p=0.048, p=0.026, and p=0.038 respectively). Stratified analyses of these interactions are presented in Appendix Table O-2-7. Model 3 also was adjusted for age, race, and current cigarette smoking. After removing the interactions from the adjusted model, marginally significant differences in mean CD16+56 cell counts was detected between Comparisons and Ranch Hands in the low and low plus high dioxin categories (Table 19-10(f): p=0.063 and p=0.097). Comparisons had a higher mean CD16+56 cell count (248.0 cells/mm^3) than Ranch Hands (low: 219.3 cells/mm^3; low plus high: 228.4 cells/mm^3). When occupation was removed from the Model 3 final adjusted model, the low plus high Ranch Hand versus Comparison contrast became nonsignificant (Appendix Table O-3-7(b): p=0.115).

None of the unadjusted or adjusted analyses of Models 4 through 6 revealed a significant relationship between current dioxin and CD16+56 cell counts (Table 19-10(g,h): p>0.66). Each of Models 4 through 6 were adjusted for age and current cigarette smoking.

CD20 Cells

The unadjusted Model 1 analysis of CD20 cell counts did not display a significant difference between Ranch Hands and Comparisons (Table 19-11(a): p>0.15). The adjusted Model 1 analysis detected a significant interaction between group and lifetime alcohol history (Table 19-11(b): p=0.024). Stratified analyses of this interaction are presented in Appendix Table O-2-8. The adjusted Model 1 analysis also accounted for age, occupation, current cigarette smoking, and current alcohol use. After removing the interaction from the model, the Model 1 analysis detected a marginally significant overall difference in mean CD20 cell counts between Ranch Hands and Comparisons (Table 19-11(b): p=0.083). Ranch Hands had a higher mean CD20 cell count (232.9 cells/mm^3) than Comparisons (218.3 cells/mm^3).

The unadjusted Model 2 analysis revealed a marginally significant positive association between initial dioxin and CD20 cell counts (Table 19-11(c): p=0.079). Mean CD20 cell counts for Ranch Hands in the low, medium, and high initial dioxin categories were 199.1, 233.4, and 241.0 cells/mm^3. The adjusted Model 2 analysis detected a significant interaction between initial dioxin and age (Table 19-11(d): p=0.049). Stratified analyses of this interaction are presented in Appendix Table O-2-8. Model 2 also was adjusted for current cigarette smoking, lifetime alcohol history, and current alcohol use. After removal of the interaction with initial dioxin, the adjusted Model 2 analysis was nonsignificant (Table 19-11(d): p=0.783). Similarly, the unadjusted Model 3 analysis did not reveal any significant associations between categorized dioxin and CD20 cell counts (Table 19-11(e): p>0.10). However, the adjusted Model 3 analysis detected a significant difference in mean CD20 cell counts between Comparisons and Ranch Hands in the background category (Table 19-11(f): p=0.013). Ranch Hands had a higher mean CD20 cell count (245.1 cells/mm^3) than Comparisons (214.0 cells/mm^3). Age, occupation, current cigarette smoking, and current alcohol use were included in the Model 3 adjusted analysis.

None of the unadjusted or adjusted analyses of Models 4 through 6 revealed a significant relationship between current dioxin and CD20 cell counts (Table 19-11(g,h):

Table 19-11.
Analysis of CD20 Cells (cells/mm³)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	Group	n	Mean[a]	Difference of Means (95% C.I.)[b]	p-Value[c]
All	***Ranch Hand***	***367***	***228.6***	***11.3 --***	***0.194***
	Comparison	***482***	***217.2***		
Officer	Ranch Hand	154	206.6	16.8 --	0.159
	Comparison	176	189.8		
Enlisted Flyer	Ranch Hand	66	228.8	-7.1 --	0.771
	Comparison	83	235.9		
Enlisted Groundcrew	Ranch Hand	147	253.9	19.6 --	0.154
	Comparison	223	234.3		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	Group	n	Adj. Mean[a]	Difference of Adj. Means (95% C.I.)[b]	p-Value[c]	Covariate Remarks[d]
All	***Ranch Hand***	***361***	***232.9*****	***14.6 --*****	0.083**	GROUP*DRKYR (p=0.024)
	Comparison	***475***	***218.3*****			AGE (p<0.001)
Officer	Ranch Hand	153	222.6**	19.2 --**	0.129**	OCC (p=0.117)
	Comparison	173	203.4**			CSMOK (p<0.001)
Enlisted Flyer	Ranch Hand	63	234.6**	-2.3 --**	0.914**	ALC (p=0.030)
	Comparison	83	236.9**			
Enlisted Groundcrew	Ranch Hand	145	235.9**	16.3 --**	0.211**	
	Comparison	219	219.6**			

[a] Transformed from the natural logarithm (x + 1) scale.

[b] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm (x + 1) scale.

[c] P-values based on difference of means on natural logarithm (x + 1) scale.

[d] Covariates and associated p-values correspond to final model based on all participants with available data.

** Group-by-covariate interaction (0.01 < p ≤ 0.05); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-8 for further analysis of this interaction.

Table 19-11. (Continued)
Analysis of CD20 Cells (cells/mm^3)

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED						
Initial Dioxin Category Summary Statistics				Analysis Results for Log_2 (Initial Dioxin)[b]		
Initial Dioxin	n	Mean[a]	Adj. Mean[ab]	R^2	Slope (Std. Error)[c]	p-Value
Low	64	196.4	199.1	0.036	0.058 (0.033)	0.079
Medium	67	232.1	233.4			
High	72	245.1	241.0			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	64	225.3**	0.204	-0.009 (0.033)**	0.783**	INIT*AGE (p=0.049)
Medium	65	226.6**				CSMOK (p<0.001)
						DRKYR (p=0.058)
High	71	215.9**				ALC (p=0.010)

[a] Transformed from natural logarithm (x + 1) scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Slope and standard error based on natural logarithm (x + 1) of CD20 cells versus $\log_2$ (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

** Log_2 (initial dioxin)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-8 for further analysis of this interaction.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-11. (Continued)
Analysis of CD20 Cells (cells/mm³)

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED					
Dioxin Category	n	Mean[a]	Adj. Mean[ab]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]
Comparison	404	213.6	213.5		
Background RH	141	227.2	228.9	15.4 --	0.203
Low RH	95	209.9	210.8	-2.7 --	0.836
High RH	108	238.2	235.4	21.9 --	0.105
Low plus High RH	203	224.5	223.5	10.0 --	0.336

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED					
Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	400	214.0			AGE ($p<0.001$) OCC ($p=0.070$) CSMOK ($p<0.001$) ALC ($p=0.010$)
Background RH	140	245.1	31.1 --	0.013	
Low RH	95	223.9	9.9 --	0.452	
High RH	106	220.2	6.2 --	0.628	
Low plus High RH	201	222.0	8.0 --	0.424	

[a] Transformed from natural logarithm (x + 1) scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Difference of adjusted means after transformation to original scale; confidence interval on difference of adjusted means not presented because analysis was performed on natural logarithm (x + 1) scale.

[d] P-value is based on difference of means on natural logarithm (x + 1) scale.

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-11. (Continued)
Analysis of CD20 Cells (cells/mm³)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[b]	Low	Medium	High	R^2	Slope (Std. Error)[c]	p-Value
4	222.9 (116)	215.0 (107)	238.2 (121)	0.003	0.022 (0.020)	0.280
5	225.1 (112)	212.1 (116)	240.6 (116)	0.004	0.021 (0.018)	0.250
6[d]	227.8 (112)	212.3 (116)	237.5 (116)	0.006	0.014 (0.019)	0.473

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[b]	Low	Medium	High	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
4	259.8 (115)	252.8 (107)	259.4 (119)	0.136	0.008 (0.020)	0.696	AGE (p=0.001) RACE (p=0.018) CSMOK (p<0.001) PACKYR (p=0.064) ALC (p=0.007)
5	263.3 (111)	247.2 (116)	266.2 (114)	0.137	0.012 (0.017)	0.480	AGE (p=0.002) RACE (p=0.018) CSMOK (p<0.001) PACKYR (p=0.065) ALC (p=0.007)
6[e]	270.6 (111)	250.0 (116)	262.7 (114)	0.142	0.002 (0.019)	0.927	AGE (p=0.001) RACE (p=0.012) CSMOK (p<0.001) PACKYR (p=0.094) ALC (p=0.005)

[a] Transformed from natural logarithm (x + 1) scale.

[b] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[c] Slope and standard error based on natural logarithm (x + 1) of CD20 cells versus log_2 (current dioxin + 1).

[d] Adjusted for log_2 total lipids.

[e] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

p>0.25). Each of Models 4 through 6 were adjusted for age, race, current cigarette smoking, lifetime smoking history, and current alcohol use.

CD25 Cells

The unadjusted Model 1 analysis of CD25 cell counts were nonsignificant (Table 19-12(a): $p>0.16$). The adjusted Model 1 analysis detected a significant interaction between group and occupation (Table 19-12(b): $p=0.022$). Analyses stratified by occupation detected a significant difference in mean CD25 cell counts between enlisted flyer Ranch Hands and Comparisons (Table 19-12(b): $p=0.015$). Ranch Hand enlisted flyers had a lower mean CD25 cell count (241.5 cells/mm^3) than Comparison enlisted flyers (291.4 cells/mm^3). Model 3 was also adjusted for race, current cigarette smoking, lifetime smoking history, and current alcohol use. After removing the interaction from the adjusted model, no significant overall difference was revealed between all Ranch Hands and Comparisons (Table 19-12(a): $p=0.936$).

The unadjusted and adjusted Model 2 analyses as well as the unadjusted Model 3 analysis were nonsignificant (Table 19-12(c,d,e): $p>0.54$). The adjusted Model 2 analysis accounted for race, current cigarette smoking, and the physical activity index. The adjusted Model 3 analysis detected a significant interactions between categorized dioxin and age, occupation, lifetime smoking history, and lifetime alcohol history (Table 19-12(f): $p=0.022$, $p=0.013$, $p=0.044$, and $p=0.016$ respectively). For further investigation of these interactions, the results of stratified analyses are presented in Appendix Table O-2-9. Race and current cigarette smoking also were accounted for in the adjusted Model 3 analysis. After removing the interactions from the model, no significant association was detected between categorized dioxin and CD25 cell counts (Table 19-12(f): $p>0.54$).

The unadjusted analysis of Models 4 through 6 did not show any significant relationships between current dioxin and CD25 cell counts (Table 19-12(g): $p>0.48$). Similarly, after adjusting for race, current cigarette smoking, lifetime smoking history, and, in Model 4, the physical activity index, the results of Models 4 and 5 remained nonsignificant (Table 19-12(h): $p>0.76$). The adjusted Model 6 analysis of CD5 cell counts revealed a significant interaction between current dioxin and lifetime smoking history (Table 19-12(h): $p=0.034$). Stratified analyses of this interaction are presented in Appendix Table O-2-9. Model 6 also was adjusted for race, current cigarette smoking, and the physical activity index. After removing the interaction from the adjusted model, the Model 6 analysis of CD25 cell counts was nonsignificant (Table 19-12(h): $p=0.449$).

CD4-CD8 Ratio

The Model 1 unadjusted analyses of the CD4-CD8 ratio did not exhibit any significant differences between Ranch Hands and Comparisons (Table 19-13(a): $p>0.29$). The adjusted Model 1 analysis revealed a significant interaction between group and the physical activity index (Table 19-13(b): $p=0.027$). For further investigation of this interaction, stratified analyses are presented in Appendix Table O-2-10. Age, occupation, current cigarette smoking, lifetime smoking history, and lifetime alcohol history also were significant in the

Table 19-12.
Analysis of CD25 Cells (cells/mm^3)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Mean[ab]**	**Difference of Means (95% C.I.)[c]**	**p-Value[d]**
All	***Ranch Hand***	***367***	***256.9***	***0.5 --***	***0.953***
	Comparison	***482***	***256.4***		
Officer	Ranch Hand	154	250.9	18.7 --	0.213
	Comparison	176	232.2		
Enlisted Flyer	Ranch Hand	66	227.6	-33.7 --	0.244
	Comparison	83	261.3		
Enlisted Groundcrew	Ranch Hand	147	280.6	21.7 --	0.163
	Comparison	223	258.9		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	**Group**	**n**	**Adj. Mean[ae]**	**Difference of Adj. Means (95% C.I.)[c]**	**p-Value[d]**	**Covariate Remarks[f]**
All	***Ranch Hand***	***367***	***276.3*****	***0.8 --*****	0.936**	GROUP*OCC (p=0.022)
	Comparison	***481***	***275.5*****			
Officer	Ranch Hand	154	277.6	7.3 --	0.605	RACE (p=0.016)
	Comparison	176	270.3			CSMOK (p<0.001)
Enlisted Flyer	Ranch Hand	66	241.5	-49.9 --	0.015	ALC (p=0.132) PACKYR (p=0.003)
	Comparison	83	291.4			
Enlisted Groundcrew	Ranch Hand	147	295.4	17.3 --	0.228	
	Comparison	222	278.1			

[a] Transformed from the natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[c] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

[d] P-values based on difference of means on natural logarithm scale.

[e] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

[f] Covariates and associated p-values correspond to final model based on all participants with available data.

** Group-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of this interaction.

Table 19-12. (Continued)
Analysis of CD25 Cells (cells/mm^3)

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED						
Initial Dioxin Category Summary Statistics				Analysis Results for Log_2 (Initial Dioxin)[b]		
Initial Dioxin	n	Mean[a]	Adj. Mean[ab]	R^2	Slope (Std. Error)[c]	p-Value
Low	64	231.1	233.7	0.511	0.021 (0.035)	0.540
Medium	67	256.4	259.6			
High	72	261.7	258.7			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	64	279.5	0.596	-0.012 (0.033)	0.729	RACE (p=0.046) CSMOK (p=0.001) PHYACT (p=0.048)
Medium	67	279.1				
High	72	276.1				

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

[c] Slope and standard error based on natural logarithm of CD25 cells versus $\log_2$ (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-12. (Continued)
Analysis of CD25 Cells (cells/mm^3)

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED					
Dioxin Category	n	Mean[a]	Adj. Mean[ab]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]
Comparison	404	248.9	248.8		
Background RH	141	252.6	254.0	5.2 --	0.680
Low RH	95	243.5	244.2	-4.6 --	0.753
High RH	108	256.8	255.2	6.4 --	0.647
Low plus High RH	203	250.5	250.0	1.2 --	0.913

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED					
Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	399	268.2**			DXCAT*AGE (p=0.022) DXCAT*OCC (p=0.013) DXCAT*PACKYR (p=0.044) DXCAT*DRKYR (p=0.016) RACE (p=0.085) CSMOK (p<0.001)
Background RH	139	276.4**	8.2 --**	0.540**	
Low RH	94	266.9**	-1.3 --**	0.933**	
High RH	106	270.1**	1.9 --**	0.895**	
Low plus High RH	200	268.6**	0.4 --**	0.970**	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

[c] Difference of adjusted means after transformation to original scale; confidence interval on difference of adjusted means not presented because analysis was performed on natural logarithm scale.

[d] P-value is based on difference of means on natural logarithm scale.

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

** Categorized dioxin-by-covariate interactions ($0.01 < p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of these interactions; refer to Appendix Table O-2-9 for further analysis of these interactions.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-12. (Continued)
Analysis of CD25 Cells (cells/mm^3)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean[ab]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[c]	Low	Medium	High	R^2	Slope (Std. Error)[d]	p-Value
4	239.1 (116)	258.8 (107)	245.3 (121)	0.363	-0.004 (0.021)	0.848
5	248.2 (112)	242.1 (116)	252.7 (116)	0.363	-0.001 (0.019)	0.960
6[e]	254.2 (112)	242.8 (116)	248.0 (116)	0.370	-0.014 (0.020)	0.482

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean[af]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[c]	Low	Medium	High	R^2	Adj. Slope (Std. Error)[d]	p-Value	Covariate Remarks
4	257.5 (116)	278.8 (107)	258.7 (121)	0.457	-0.006 (0.020)	0.762	RACE (p=0.075) CSMOK (p<0.001) PACKYR (p=0.018) PHYACT (p=0.146)
5	282.2 (112)	268.7 (116)	284.6 (116)	0.448	0.002 (0.017)	0.915	RACE (p=0.047) CSMOK (p<0.001) PACKYR (p=0.023)
6[e]	281.0** (112)	264.4** (116)	268.5** (116)	0.472	-0.014 (0.019)**	0.449**	CURR*PACKYR (p=0.034) RACE (p=0.044) CSMOK (p<0.001) PACKYR (p=0.007) PHYACT (p=0.078)

[a] Transformed from natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[c] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[d] Slope and standard error based on natural logarithm of CD25 cells versus log_2 (current dioxin + 1).

[e] Adjusted for log_2 total lipids.

[f] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

** Log_2 (current dioxin + 1)-by-covariate interaction ($0.01<p\leq0.05$); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-9 for further analysis of this interaction.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 19-13.
Analysis of CD4-CD8 Ratio

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Mean[a]**	**Difference of Means (95% C.I.)[b]**	**p-Value[c]**
All	***Ranch Hand***	***367***	***1.534***	***0.047 --***	***0.295***
	Comparison	***482***	***1.487***		
Officer	Ranch Hand	154	1.538	0.037 --	0.631
	Comparison	176	1.501		
Enlisted Flyer	Ranch Hand	66	1.517	0.085 --	0.367
	Comparison	83	1.432		
Enlisted Groundcrew	Ranch Hand	147	1.536	0.039 --	0.549
	Comparison	223	1.497		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	**Group**	**n**	**Adj. Mean[a]**	**Difference of Adj. Means (95% C.I.)[b]**	**p-Value[c]**	**Covariate Remarks[d]**
All	***Ranch Hand***	***361***	***1.532*****	***0.062 --*****	0.154**	GROUP*PHYACT (p=0.027)
	Comparison	***475***	***1.470*****			AGE (p<0.001)
Officer	Ranch Hand	153	1.605**	0.060 --**	0.417**	OCC (p=0.044)
	Comparison	173	1.545**			CSMOK (p=0.077)
Enlisted Flyer	Ranch Hand	63	1.549**	0.136 --**	0.186**	PACKYR (p=0.119)
	Comparison	83	1.413**			DRKYR (p=0.132)
Enlisted Groundcrew	Ranch Hand	145	1.469**	0.035 --**	0.584**	
	Comparison	219	1.434**			

[a] Transformed from the natural logarithm scale.

[b] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

[c] P-values based on difference of means on natural logarithm scale.

[d] Covariates and associated p-values correspond to final model based on all participants with available data.

** Group-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-10 for further analysis of this interaction.

Table 19-13. (Continued)
Analysis of CD4-CD8 Ratio

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED						
Initial Dioxin Category Summary Statistics				Analysis Results for Log_2 (Initial Dioxin)[b]		
Initial Dioxin	n	Mean[a]	Adj. Mean[ab]	R^2	Slope (Std. Error)[c]	p-Value
Low	64	1.506	1.516	0.008	0.004 (0.025)	0.881
Medium	67	1.572	1.577			
High	72	1.569	1.556			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	64	1.594	0.072	-0.017 (0.026)	0.526	AGE (p=0.071) CSMOK (p=0.043) ALC (p=0.031)
Medium	66	1.583				
High	71	1.510				

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Slope and standard error based on natural logarithm of CD4-CD8 ratio versus log_2 (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-13. (Continued)
Analysis of CD4-CD8 Ratio

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED					
Dioxin Category	n	Mean[a]	Adj. Mean[ab]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]
Comparison	404	1.488	1.488		
Background RH	141	1.500	1.504	0.016 --	0.799
Low RH	95	1.532	1.541	0.053 --	0.470
High RH	108	1.566	1.553	0.065 --	0.357
Low plus High RH	203	1.550	1.548	0.060 --	0.286

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED					
Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	399	1.479			AGE (p=0.002) OCC (p=0.124) CSMOK (p=0.002) DRKYR (p=0.050)
Background RH	139	1.499	0.020 --	0.756	
Low RH	94	1.576	0.097 --	0.185	
High RH	106	1.566	0.087 --	0.222	
Low plus High RH	200	1.571	0.092 --	0.097	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Difference of adjusted means after transformation to original scale; confidence interval on difference of adjusted means not presented because analysis was performed on natural logarithm scale.

[d] P-value is based on difference of means on natural logarithm scale.

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-13. (Continued)
Analysis of CD4-CD8 Ratio

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[b]	Low	Medium	High	R^2	Slope (Std. Error)[c]	p-Value
4	1.495 (116)	1.485 (107)	1.604 (121)	0.001	0.011 (0.016)	0.510
5	1.531 (112)	1.466 (116)	1.593 (116)	0.003	0.014 (0.014)	0.338
6[d]	1.559 (112)	1.469 (116)	1.564 (116)	0.013	0.003 (0.015)	0.833

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[b]	Low	Medium	High	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
4	1.510 (115)	1.510 (107)	1.588 (119)	0.022	0.003 (0.017)	0.868	AGE (p=0.031) ALC (p=0.095)
5	1.547 (111)	1.490 (116)	1.575 (114)	0.022	0.006 (0.015)	0.657	AGE (p=0.036) ALC (p=0.100)
6[e]	1.572 (111)	1.494 (116)	1.547 (114)	0.030	-0.003 (0.016)	0.833	AGE (p=0.027) ALC (p=0.126)

[a] Transformed from natural logarithm scale.

[b] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[c] Slope and standard error based on natural logarithm of CD4-CD8 ratio versus log_2 (current dioxin + 1).

[d] Adjusted for log_2 total lipids.

[e] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = $\leq$ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = $\leq$ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

adjusted Model 1 analysis. The results of the Model 1 analysis after removal of the interaction with group were nonsignificant (Table 19-13(b): $p>0.15$).

The unadjusted and adjusted Model 2 analyses as well as the unadjusted Model 3 analyses of the CD4-CD8 ratio did not exhibit any significant associations between the CD4-CD8 ratio and dioxin (Table 19-13(c-e): $p>0.28$). The adjusted Model 2 analysis accounted for age, current cigarette smoking, and current alcohol use. The Model 3 adjusted analysis of the CD4-CD8 ratio detected a marginally significant difference between Comparisons and Ranch Hands in the low plus high initial dioxin category (Table 19-13(f): $p=0.097$). Ranch Hands had a higher mean CD4-CD8 ratio (1.571) than Comparisons (1.479). Model 3 was adjusted for age, occupation, current cigarette smoking, and lifetime alcohol history. After occupation was removed from the Model 3 final adjusted model, the low plus high Ranch Hand versus Comparison contrast was nonsignificant (Appendix Table O-3-10(a): $p=0.161$).

None of the unadjusted or adjusted analyses of Models 4 through 6 revealed a significant relationship between current dioxin and the CD4-CD8 ratio (Table 19-13(g,h): $p>0.33$). Each of Models 4 through 6 were adjusted for age and current alcohol use.

Double Labelled Cells: CD3 with CD25

The unadjusted Model 1 analysis of CD3 with CD25 revealed no significant differences between Ranch Hands and Comparisons (Table 19-14(a): $p>0.10$ for all occupational categories). In the adjusted analysis, the group-by-occupation interaction was significant (Table 19-14(b): $p=0.029$). The difference in CD3 with CD25 means between Ranch Hands and Comparisons was significant for enlisted flyers ($p=0.022$) but not for officers and enlisted flyers ($p=0.783$ and $p=0.185$ respectively). Among the enlisted flyers, the adjusted CD3 with CD25 means were 190.6 cells/mm^3 for Ranch Hands and 229.4 cells/mm^3 for Comparisons. After removing the group-by-occupation interaction, there was no significant difference between all Ranch Hands and Comparisons ($p=0.949$). Significant covariates retained in the adjusted model were race, current cigarette smoking, and lifetime cigarette smoking history.

In Model 2, the association between initial dioxin and CD3 with CD25 was not significant for the unadjusted and adjusted analyses (Table 19-14(c,d): $p=0.891$ and $p=0.422$). Covariates retained in the final adjusted model were race, current cigarette smoking, and the physical activity index.

No significant results were found in the unadjusted Model 3 analysis of CD3 with CD25 (Table 19-14(e): $p>0.61$ for all contrasts). The adjusted model contained significant interactions of categorized dioxin with occupation, lifetime cigarette smoking history, and lifetime alcohol history (Table 19-14(f): $p=0.008$, $p=0.023$, and $p=0.004$). Stratified results, investigating these interactions, are presented in Appendix Table O-2-11. After removing the interactions from the final model, no significant results were found ($p>0.45$ for all contrasts). Race and current cigarette smoking also were significant covariates in the adjusted model.

Table 19-14.
Analysis of Double Labelled Cells: CD3 with CD25 (cells/mm^3)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	Group	n	Mean[ab]	Difference of Means (95% C.I.)[c]	p-Value[d]
All	***Ranch Hand***	***367***	***202.6***	***0.3 --***	***0.966***
	Comparison	***482***	***202.3***		
Officer	Ranch Hand	154	195.9	14.1 --	0.250
	Comparison	176	181.9		
Enlisted Flyer	Ranch Hand	66	175.2	-31.8 --	0.151
	Comparison	83	207.0		
Enlisted Groundcrew	Ranch Hand	147	226.0	21.8 --	0.102
	Comparison	223	204.2		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	Group	n	Adj. Mean[ae]	Difference of Adj. Means (95% C.I.)[c]	p-Value[d]	Covariate Remarks[f]
All	***Ranch Hand***	***367***	***218.8*****	***0.5 --*****	0.949**	GROUP*OCC (p=0.029)
	Comparison	***481***	***218.3*****			RACE (p=0.014)
Officer	Ranch Hand	154	217.8	3.1 --	0.783	CSMOK (p<0.001)
	Comparison	176	214.6			PACKYR (p=0.001)
Enlisted Flyer	Ranch Hand	66	190.6	-38.8 --	0.022	
	Comparison	83	229.4			
Enlisted Groundcrew	Ranch Hand	147	237.1	16.0 --	0.185	
	Comparison	222	221.1			

[a] Transformed from the natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[c] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

[d] P-values based on difference of means on natural logarithm scale.

[e] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

[f] Covariates and associated p-values correspond to final model based on all participants with available data.

** Group-by-covariate interaction (0.01<p≤0.05); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-11 for further analysis of this interaction.

Table 19-14. (Continued)
Analysis of Double Labelled Cells: CD3 with CD25 ($cells/mm^3$)

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED						
Initial Dioxin Category Summary Statistics				Analysis Results for Log_2 (Initial Dioxin)[b]		
Initial Dioxin	n	Mean[a]	Adj. Mean[ab]	R^2	Slope (Std. Error)[c]	p-Value
Low	64	186.0	188.9	0.511	0.005 (0.038)	0.891
Medium	67	206.0	209.7			
High	72	201.3	198.1			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	64	225.9	0.587	-0.029 (0.036)	0.422	RACE (p=0.078) CSMOK (p=0.001) PHYACT (p=0.087)
Medium	67	223.9				
High	72	210.2				

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

[c] Slope and standard error based on natural logarithm of CD3 with CD25 cells versus log_2 (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-14. (Continued)
Analysis of Double Labelled Cells: CD3 with CD25 (cells/mm^3)

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED					
Dioxin Category	n	Mean[a]	Adj. Mean[ab]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]
Comparison	404	196.1	196.0		
Background RH	141	199.7	201.1	5.1 --	0.635
Low RH	95	193.2	193.7	-2.3 --	0.850
High RH	108	203.5	202.0	6.0 --	0.614
Low plus High RH	203	198.6	198.1	2.1 --	0.827

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED					
Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	399	212.7**			DXCAT*OCC (p=0.008) DXCAT*PACKYR (p=0.023) DXCAT*DRKYR (p=0.004) RACE (p=0.043) CSMOK (p<0.001)
Background RH	139	221.1**	8.4 --**	0.456**	
Low RH	94	211.6**	-1.1 --**	0.931**	
High RH	106	215.3**	2.6 --**	0.827**	
Low plus High RH	200	213.5**	0.8 --**	0.926**	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

[c] Difference of adjusted means after transformation to original scale; confidence interval on difference of adjusted means not presented because analysis was performed on natural logarithm scale.

[d] P-value is based on difference of means on natural logarithm scale.

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

** Categorized dioxin-by-covariate interactions ($p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of these interactions; refer to Appendix Table O-2-11 for further analysis of these interactions.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-14. (Continued)
Analysis of Double Labelled Cells: CD3 with CD25 (cells/mm^3)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean[ab]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[c]	Low	Medium	High	R^2	Slope (Std. Error)[d]	p-Value
4	186.0 (116)	207.7 (107)	193.1 (121)	0.365	-0.007 (0.023)	0.750
5	194.6 (112)	192.3 (116)	199.1 (116)	0.365	-0.004 (0.020)	0.859
6[e]	199.4 (112)	192.9 (116)	195.3 (116)	0.372	-0.018 (0.022)	0.414

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean[af]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[c]	Low	Medium	High	R^2	Adj. Slope (Std. Error)[d]	p-Value	Covariate Remarks
4	206.6 (116)	229.7 (107)	213.3 (121)	0.449	-0.005 (0.022)	0.826	RACE (p=0.066) CSMOK (p<0.001) PACKYR (p=0.013)
5	221.1 (112)	212.6 (116)	224.2 (116)	0.449	-0.000 (0.019)	0.986	RACE (p=0.068) CSMOK (p<0.001) PACKYR (p=0.012)
6[e]	220.4 (112)	209.5 (116)	211.4 (116)	0.471	-0.017 (0.020)**	0.397**	CURR*PACKYR (p=0.042) RACE (p=0.061) CSMOK (p<0.001) PHYACT (p=0.098)

[a] Transformed from natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[c] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[d] Slope and standard error based on natural logarithm of CD3 with CD25 cells versus log_2 (current dioxin + 1).

[e] Adjusted for log_2 total lipids.

[f] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

** Log_2 (current dioxin + 1)-by-covariate interaction ($0.01<p\leq0.05$); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-11 for further analysis of this interaction.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

No significant associations between current dioxin and CD3 with CD25 were found in the unadjusted and adjusted analyses of Models 4, 5, and 6 (Table 19-14(g,h): $p>0.39$ for all analyses). The adjusted Model 6 analysis revealed a significant current dioxin-by-lifetime cigarette smoking history interaction ($p=0.042$). Stratified results are presented in Appendix Table O-2-11. Race, current cigarette smoking, and lifetime cigarette smoking were included in the adjusted analyses for Models 4 and 5. In Model 6, race, current cigarette smoking, and the physical activity index were retained in the final model.

Double Labelled Cells: CD5 with CD20 Cells

Because 4.7 percent (40/849) of the CD5 with CD20 measurements were 0 cells/mm^3, the analysis was conducted in two parts. First, the proportion of CD5 with CD20 cell counts equal to 0 was examined for an association with exposure. Second, only nonzero measurements were explored for an association with exposure.

For Model 1 analysis, no associations between the proportion of CD5 with CD20 cell counts equal to zero and group were observed (Table 19-15(a1,b1): $p\geq0.31$).

Based on the nonzero CD5 with CD20 cells counts, the Model 1 unadjusted analysis detected a significant difference between Ranch Hand and Comparison enlisted groundcrew (Table 19-15(a2): $p=0.046$). Ranch Hand enlisted groundcrew had a significantly higher mean CD5 with CD20 cell count (65.2 cells/mm^3) than Comparison enlisted groundcrew (54.7 cells/mm^3). However, after adjusting for age and current alcohol use, the Model 1 results were nonsignificant (Table 19-15(b2): $p>0.16$ for all contrasts).

The unadjusted Model 2 analysis of the dichotomized CD5 with CD20 cell counts was nonsignificant (Table 19-15(c2): $p=0.248$). However, after adjusting for current cigarette smoking, lifetime cigarette smoking history, and lifetime alcohol history, the Model 2 analysis showed a marginally significant negative association between the proportion of zero CD5 with CD20 cell counts and initial dioxin (Table 19-15(d1): $p=0.068$, Adj. RR=0.57).

The Model 2 unadjusted and adjusted analyses did not reveal a significant association between nonzero CD5 with CD20 measurements and initial dioxin (Table 19-15(c2,d2): $p>0.13$). The Model 2 analysis was adjusted for age, current cigarette smoking, lifetime cigarette smoking history, current alcohol use, and the physical activity index.

No significant associations were found between the proportion of zero CD5 with CD20 cell counts and categorized dioxin or current dioxin (Table 19-15(e1-h1): $p>0.12$ for all unadjusted and adjusted contrasts).

The Model 3 unadjusted analysis detected a marginally significant difference in mean CD5 with CD20 cell counts between Ranch Hands in the high initial dioxin category and Comparisons (Table 19-15(e2): $p=0.084$, 59.2 cells/mm^3 versus 50.6 cells/mm^3 respectively). After adjusting for age and current alcohol use, the Model 3 results were nonsignificant (Table 19-15(f2): $p>0.11$).

Table 19-15.
Analysis of Double Labelled Cells: CD5 with CD20
(Zero vs. Nonzero)

a1) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Percent Zero**	**Est. Relative Risk (95% C.I.)**	**p-Value**
All	*Ranch Hand*	*367*	*5.2*	*1.20 (0.64,2.26)*	*0.693*
	Comparison	*482*	*4.4*		
Officer	Ranch Hand	154	6.5	1.04 (0.43,2.52)	0.999
	Comparison	176	6.2		
Enlisted Flyer	Ranch Hand	66	3.0	0.62 (0.11,3.48)	0.895
	Comparison	83	4.8		
Enlisted Groundcrew	Ranch Hand	147	4.8	1.81 (0.60,5.49)	0.441
	Comparison	223	2.7		

b1) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	**Adj. Relative Risk (95% C.I.)**	**p-Value**	**Covariate Remarks[a]**
All	*1.18 (0.62,2.24)*	*0.625*	AGE (p<0.001)
Officer	1.06 (0.43,2.61)	0.906	PACKYR (p=0.033)
Enlisted Flyer	0.64 (0.11,3.64)	0.613	CSMOK (p=0.080)
Enlisted Groundcrew	1.80 (0.58,5.60)	0.310	ALC (p=0.138)

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-15. (Continued)
Analysis of Double Labelled Cells: CD5 with CD20 (cells/mm^3)
(Nonzero Measurements)

a2) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	Group	n	Mean[a]	Difference of Means (95% C.I.)[b]	p-Value[c]
All	*Ranch Hand*	*348*	*54.2*	*2.4 --*	*0.424*
	Comparison	*461*	*51.8*		
Officer	Ranch Hand	144	47.9	3.6 --	0.430
	Comparison	165	44.3		
Enlisted Flyer	Ranch Hand	64	48.0	-2.6 --	0.802
	Comparison	79	50.6		
Enlisted Groundcrew	Ranch Hand	140	65.2	10.5 --	0.046
	Comparison	217	54.7		

b2) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	Group	n	Adj. Mean[a]	Difference of Adj. Means (95% C.I.)[b]	p-Value[c]	Covariate Remarks[d]
All	*Ranch Hand*	*345*	*55.1*	*4.2 --*	0.162	AGE ($p<0.001$)
	Comparison	*456*	*50.9*			ALC ($p=0.006$)
Officer	Ranch Hand	144	52.8	4.4 --	0.342	
	Comparison	163	48.4			
Enlisted Flyer	Ranch Hand	62	53.0	-0.6 --	0.939	
	Comparison	79	53.6			
Enlisted Groundcrew	Ranch Hand	139	58.6	6.6 --	0.174	
	Comparison	214	52.1			

[a] Transformed from the natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[c] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

[d] P-values based on difference of means on natural logarithm scale.

[e] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

[f] Covariates and associated p-values correspond to final model based on all participants with available data.

Note: Analysis based on measurements above 0 cells/mm^3 only.

Table 19-15. (Continued)
Analysis of Double Labelled Cells: CD5 with CD20
(Zero vs. Nonzero)

c1) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Zero	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	64	7.8	0.72 (0.41,1.29)	0.248
Medium	67	6.0		
High	72	4.2		

d1) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)[c]			
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
200	0.57 (0.30,1.09)	0.068	PACKYR (p<0.001) DRKYR (p=0.087) CSMOK (p=0.008)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-15. (Continued)
Analysis of Double Labelled Cells: CD5 with CD20 (cells/mm^3)
(Nonzero Measurements)

c2) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED						
Initial Dioxin Category Summary Statistics				Analysis Results for Log_2 (Initial Dioxin)[b]		
Initial Dioxin	n	Mean[a]	Adj. Mean[ab]	R^2	Slope (Std. Error)[c]	p-Value
Low	59	48.1	49.6	0.457	0.089 (0.058)	0.131
Medium	63	59.4	61.4			
High	69	64.1	62.0			

d2) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	59	62.4	0.533	-0.040 (0.066)	0.542	AGE (p=0.066) CSMOK (p=0.030)
Medium	62	57.9				PACKYR (p=0.117) ALC (p=0.038)
High	68	52.0				PHYACT (p=0.134)

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

[c] Slope and standard error based on natural logarithm of CD5 with CD20 versus log_2 (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

Note: Analysis based on measurements above 0 cells/mm^3 only.
Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-15. (Continued)
Analysis of Double Labelled Cells: CD5 with CD20
(Zero vs. Nonzero)

e1) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Zero	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	404	4.5		
Background RH	141	2.8	0.52 (0.17,1.58)	0.246
Low RH	95	8.4	1.96 (0.81,4.72)	0.134
High RH	108	3.7	0.96 (0.31,2.93)	0.939
Low plus High RH	203	5.9	1.45 (0.68,3.12)	0.338

f1) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	400			AGE (p<0.001) PACKYR (p=0.010) CSMOK (p=0.072) ALC (p=0.078)
Background RH	140	0.49 (0.16,1.53)	0.219	
Low RH	95	2.05 (0.82,5.13)	0.126	
High RH	106	1.29 (0.41,4.07)	0.666	
Low plus High RH	201	1.70 (0.77,3.77)	0.187	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-15. (Continued)
Analysis of Double Labelled Cells: CD5 with CD20 (cells/mm^3)
(Nonzero Measurements)

e2) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED					
Dioxin Category	n	Mean[a]	Adj. Mean[ab]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]
Comparison	386	49.7	50.6		
Background RH	137	48.5	49.8	-0.8 --	0.842
Low RH	87	50.3	51.8	1.2 --	0.808
High RH	104	58.8	59.2	8.6 --	0.084
Low plus High RH	191	54.8	53.7	5.1 --	0.189

f2) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED					
Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	382	49.7			AGE ($p<0.001$) ALC ($p=0.007$)
Background RH	136	51.4	1.7 --	0.681	
Low RH	87	56.2	6.5 --	0.207	
High RH	102	55.2	5.5 --	0.242	
Low plus High RH	189	55.7	6.0 --	0.115	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

[c] Difference of adjusted means after transformation to original scale; confidence interval on difference of adjusted means not presented because analysis was performed on natural logarithm scale.

[d] P-value is based on difference of means on natural logarithm scale.

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

Note: Analysis based on measurements above 0 cells/mm^3 only.
RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-15. (Continued)
Analysis of Double Labelled Cells: CD5 with CD20
(Zero vs. Nonzero)

g1) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Zero/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	2.6 (116)	6.5 (107)	5.0 (121)	1.04 (0.73,1.47)	0.834
5	3.6 (112)	4.3 (116)	6.0 (116)	1.06 (0.78,1.44)	0.699
6[c]	3.6 (112)	4.3 (116)	6.0 (116)	1.03 (0.74,1.43)	0.883

h1) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	344	1.02 (0.72,1.44)	0.912	PACKYR (p=0.054)
5	344	1.05 (0.78,1.42)	0.738	PACKYR (p=0.054)
6[d]	344	1.00 (0.72,1.39)	0.367	PACKYR (p=0.041)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = $\leq$ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = $\leq$ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 19-15. (Continued)
Analysis of Double Labelled Cells: CD5 with CD20 (cells/mm³)
(Nonzero Measurements)

g2) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean[ab]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[c]	Low	Medium	High	R^2	Slope (Std. Error)[d]	p-Value
4	48.1 (113)	48.8 (100)	62.7 (115)	0.274	0.078 (0.033)	0.017
5	50.9 (108)	45.0 (111)	65.6 (109)	0.275	0.069 (0.028)	0.016
6[e]	51.7 (108)	45.1 (111)	64.7 (109)	0.276	0.062 (0.031)	0.044

h2) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean[af]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[c]	Low	Medium	High	R^2	Adj. Slope (Std. Error)[d]	p-Value	Covariate Remarks
4	48.2 (112)	51.8 (100)	60.0 (113)	0.321	0.063 (0.033)	0.060	AGE (p=0.012) ALC (p=0.002)
5	50.9 (107)	47.0 (111)	63.9 (107)	0.322	0.058 (0.029)	0.044	AGE (p=0.011) ALC (p=0.002)
6[e]	51.8 (107)	47.2 (111)	62.7 (107)	0.324	0.048 (0.031)	0.120	AGE (p=0.010) ALC (p=0.002)

[a] Transformed from natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[c] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[d] Slope and standard error based on natural logarithm of CD5 with CD20 versus log_2 (current dioxin + 1).

[e] Adjusted for log_2 total lipids.

[f] Adjusted for examination group (batch-to-batch) variation and covarites specified under "Covariate Remarks" column.

Note: Analysis based on measurements above 0 cells/mm³ only.
Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

The unadjusted analyses of Models 4 through 6 each displayed a significant positive association between nonzero CD5 with CD20 cell counts and current dioxin (Table 19-15(g2): p=0.017, p=0.016, and p=0.044 respectively). For Model 4, the unadjusted mean CD5 with CD20 cell counts for the low, medium, and high current dioxin categories were 48.1, 48.8, and 62.7 cells/mm^3; for Model 5 the corresponding means were 50.9, 45.0, and 65.6 cells/mm^3; and for Model 6 the means were 51.7, 45.1, and 64.7 cells/mm^3. Similarly, the adjusted analysis of Model 4 revealed a marginally significant positive association between nonzero CD5 with CD20 cell counts and Model 5 displayed a significant positive association (Table 19-15(h2): p=0.060 and p=0.044 respectively). The adjusted Model 4 means for the low, medium, and high current dioxin categories were 48.2, 51.8, and 60.0 cells/mm^3. Similarly, the Model 5 adjusted means were 50.9, 47.0, and 63.9 cells/mm^3. The adjusted Model 6 analysis was nonsignificant (p=0.120). Models 4 through 6 were adjusted for age and current alcohol use.

Double Labelled Cells: CD4 with CD8 Cells

Because 10.6 percent (90/849) of the CD4 with CD8 measurements were 0 cells/mm^3, the analysis was conducted in two parts. First, the proportion of CD4 with CD8 cell counts equal to 0 was examined for an association with exposure. Second, only nonzero measurements were explored for an association with exposure.

For the first analysis, no associations between the proportion of CD4 with CD8 measurement equal to zero and group, initial dioxin, or current dioxin were observed (Table 19-16(a1-h1): p>0.26). The Model 2 adjusted analysis did detect significant interactions between initial dioxin and race and between initial dioxin and current cigarette smoking (Table 19-16(d1): p=0.016 and p=0.028). Stratified analyses of these interactions are presented in Appendix Table O-2-12.

Similarly, the analysis based on nonzero CD4 with CD8 cell counts did not find any significant associations with group, initial, or current dioxin (Table 19-16(a2-h2): p>0.19 for all analyses). The Model 2 adjusted analysis detected a significant interaction between initial dioxin and lifetime alcohol history Table 19-16(d2): p=0.020), and the Model 3 adjusted analysis detected significant categorized dioxin-by-age, categorized dioxin-by-race and categorized dioxin-by-occupation interactions (Table 19-16(f2): p=0.001, p=0.031, and p=0.029 respectively). Stratified analyses of each of these interaction are presented in Appendix Table O-2-12.

Double Labelled Cells: CD3 with CD16+56 Cells

Because 3.4 percent (29/849) of the CD3 with CD16+56 measurements were 0 cells/mm^3, the analysis was conducted in two parts. First, the proportion of CD3 with CD16+56 cell counts equal to 0 was examined for an association with exposure. Second, only nonzero measurements were explored for an association with exposure.

For Model 1, no associations between the proportion of CD3 with CD16+56 cell counts equal to zero and group were observed (Table 19-17(a1,b1): p>0.32).

Table 19-16.
Analysis of Double Labelled Cells: CD4 with CD8
(Zero vs. Nonzero)

a1) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Percent Zero**	**Est. Relative Risk (95% C.I.)**	**p-Value**
All	***Ranch Hand***	***367***	***10.6***	***1.01 (0.65,1.56)***	***0.999***
	Comparison	***482***	***10.6***		
Officer	Ranch Hand	154	11.0	1.09 (0.54,2.20)	0.952
	Comparison	176	10.2		
Enlisted Flyer	Ranch Hand	66	9.1	1.98 (0.53,7.31)	0.480
	Comparison	83	4.8		
Enlisted Groundcrew	Ranch Hand	147	10.9	0.82 (0.43,1.56)	0.654
	Comparison	223	13.0		

b1) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	**Adj. Relative Risk (95% C.I.)**	**p-Value**	**Covariate Remarks[a]**
All	***1.04 (0.67,1.62)***	***0.864***	AGE (p=0.005)
Officer	1.14 (0.56,2.30)	0.723	
Enlisted Flyer	2.12 (0.57,7.88)	0.263	
Enlisted Groundcrew	0.80 (0.42,1.54)	0.505	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-16. (Continued)
Analysis of Double Labelled Cells: CD4 with CD8 ($cells/mm^3$)
(Nonzero Measurements)

a2) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Mean[a]**	**Difference of Means (95% C.I.)[b]**	**p-Value[c]**
All	*Ranch Hand*	*328*	*30.0*	*-0.5 --*	*0.765*
	Comparison	*431*	*30.5*		
Officer	Ranch Hand	137	29.0	-1.6 --	0.498
	Comparison	158	30.6		
Enlisted Flyer	Ranch Hand	60	30.5	1.1 --	0.733
	Comparison	79	29.4		
Enlisted Groundcrew	Ranch Hand	131	30.9	0.1 --	0.946
	Comparison	194	30.8		

b2) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	**Group**	**n**	**Adj. Mean[a]**	**Difference of Adj. Means (95% C.I.)[b]**	**p-Value[c]**	**Covariate Remarks[d]**
All	*Ranch Hand*	*328*	*30.0*	*-0.4 --*	0.769	AGE (p=0.059)
	Comparison	*430*	*30.4*			CSMOK (p<0.001)
Officer	Ranch Hand	137	28.9	-1.5 --	0.498	PACKYR (p=0.030)
	Comparison	158	30.4			
Enlisted Flyer	Ranch Hand	60	29.7	0.7 --	0.814	
	Comparison	79	29.0			
Enlisted Groundcrew	Ranch Hand	131	31.3	0.2 --	0.927	
	Comparison	193	31.1			

[a] Transformed from the natural logarithm scale.

[b] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

[c] P-values based on difference of means on natural logarithm scale.

[d] Covariates and associated p-values correspond to final model based on all participants with available data.

Note: Analysis based on measurements above 0 $cells/mm^3$ only.

Table 19-16. (Continued)
Analysis of Double Labelled Cells: CD4 with CD8
(Zero vs. Nonzero)

c1) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Zero	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	64	12.5	0.93 (0.65,1.33)	0.686
Medium	67	7.5		
High	72	13.9		

d1) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)[c]			
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
200	0.96 (0.68,1.37)**	0.829**	INIT*RACE (p=0.016) INIT*CSMOK (p=0.028) DRKYR (p=0.087)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

** Log_2 (initial dioxin)-by-covariate interactions ($0.01 < p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of these interactions; refer to Appendix Table O-2-12 for further analysis of these interactions.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-16. (Continued)
Analysis of Double Labelled Cells: CD4 with CD8 (cells/mm^3)
(Nonzero Measurements)

c2) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED						
Initial Dioxin Category Summary Statistics				Analysis Results for Log$_2$ (Initial Dioxin)[b]		
Initial Dioxin	n	Mean[a]	Adj. Mean[ab]	R^2	Slope (Std. Error)[c]	p-Value
Low	56	25.6	25.7	0.006	0.036 (0.037)	0.337
Medium	62	27.3	27.4			
High	62	28.7	28.6			

d2) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log$_2$ (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	56	26.4**	0.107	0.018 (0.037)**	0.628**	INIT*DRKYR (p=0.020) CSMOK (p=0.008)
Medium	60	27.5**				
High	61	27.1**				

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Slope and standard error based on natural logarithm of CD4 with CD8 versus log$_2$ (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

** Log$_2$ (initial dioxin)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-12 for further analysis of this interaction.

Note: Analysis based on measurements above 0 cells/mm^3 only.
Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-16. (Continued)
Analysis of Double Labelled Cells: CD4 with CD8
(Zero vs. Nonzero)

e1) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED

Dioxin Category	n	Percent Zero	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	404	10.6		
Background RH	141	10.6	1.04 (0.55,1.96)	0.905
Low RH	95	10.5	1.03 (0.49,2.14)	0.945
High RH	108	12.0	1.04 (0.53,2.05)	0.902
Low plus High RH	203	11.3	1.04 (0.60,1.79)	0.900

f1) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED

Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	404			AGE (p=0.017)
Background RH	141	1.15 (0.61,2.18)	0.671	
Low RH	95	1.18 (0.56,2.49)	0.662	
High RH	108	0.94 (0.48,1.86)	0.867	
Low plus High RH	203	1.04 (0.60,1.79)	0.893	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-16. (Continued)
Analysis of Double Labelled Cells: CD4 with CD8 (cells/mm^3)
(Nonzero Measurements)

e2) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED					
Dioxin Category	n	Mean[a]	Adj. Mean[ab]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]
Comparison	361	29.4	29.4		
Background RH	126	31.5	31.7	2.35 --	0.283
Low RH	85	26.5	26.4	-3.00 --	0.190
High RH	95	27.9	27.9	-1.46 --	0.518
Low plus High RH	180	27.2	27.2	-2.20 --	0.211

f2) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED					
Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	360	31.8**			DXCAT*AGE (p=0.001) DXCAT*RACE (p=0.029) DXCAT*OCC (p=0.031) CSMOK (p<0.001) PACKYR (p=0.042)
Background RH	126	34.8**	2.93 --**	0.230**	
Low RH	85	29.0**	-2.86 --**	0.251**	
High RH	95	29.7**	-2.10 --**	0.390**	
Low plus High RH	180	29.4**	-2.46 --**	0.192**	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Difference of adjusted means after transformation to original scale; confidence interval on difference of adjusted means not presented because analysis was performed on natural logarithm scale.

[d] P-value is based on difference of means on natural logarithm scale.

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

** Categorized dioxin-by-covariate interactions ($p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of these interactions; refer to Appendix Table O-2-12 for further analysis of these interactions.

Note: Analysis based on measurements above 0 cells/mm^3 only.
RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-16. (Continued)
Analysis of Double Labelled Cells: CD4 with CD8
(Zero vs. Nonzero)

g1) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Zero/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	9.5 (116)	12.1 (107)	11.6 (121)	1.02 (0.81,1.29)	0.852
5	10.7 (112)	9.5 (116)	12.9 (116)	1.03 (0.84,1.27)	0.763
6[c]	10.7 (112)	9.5 (116)	12.9 (116)	1.02 (0.81,1.27)	0.884

h1) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	339	0.97 (0.76,1.23)	0.769	AGE (p=0.045) DRKYR (p=0.070)
5	339	0.98 (0.80,1.21)	0.882	AGE (p=0.048) DRKYR (p=0.068)
6[d]	339	0.96 (0.77,1.21)	0.736	AGE (p=0.044) DRKYR (p=0.067)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 19-16. (Continued)
Analysis of Double Labelled Cells: CD4 with CD8 (cells/mm^3)
(Nonzero Measurements)

g2) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[b]	Low	Medium	High	R^2	Slope (Std. Error)[c]	p-Value
4	31.3 (105)	27.6 (94)	27.8 (107)	0.002	-0.021 (0.027)	0.443
5	22.1 (112)	21.2 (116)	18.9 (116)	0.001	-0.021 (0.041)	0.614
6[d]	22.4 (112)	21.3 (116)	18.6 (116)	0.001	-0.028 (0.044)	0.522

h2) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[b]	Low	Medium	High	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
4	30.7 (105)	27.9 (94)	28.2 (107)	0.083	-0.011 (0.027)	0.697	AGE (p=0.071) CSMOK (p<0.001) PACKYR (p=0.045)
5	21.6 (111)	20.1 (114)	19.6 (114)	0.063	0.005 (0.041)	0.906	AGE (p=0.021) CSMOK (p=0.001) DRKYR (p=0.103)
6[e]	22.0 (111)	20.2 (114)	19.2 (114)	0.064	-0.002 (0.044)	0.956	AGE (p=0.023) CSMOK (p=0.001) DRKYR (p=0.103)

[a] Transformed from natural logarithm scale.

[b] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[c] Slope and standard error based on natural logarithm of CD4 with CD8 versus log_2 (current dioxin + 1).

[d] Adjusted for log_2 total lipids.

[e] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

Note: Analysis based on measurements above 0 cells/mm^3 only.
Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 19-17.
Analysis of Double Labelled Cells: CD3 with CD16+56
(Zero vs. Nonzero)

a1) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Percent Zero**	**Est. Relative Risk (95% C.I.)**	**p-Value**
All	*Ranch Hand*	*367*	*3.8*	*1.24 (0.59,2.59)*	*0.713*
	Comparison	*482*	*3.1*		
Officer	Ranch Hand	154	3.9	0.85 (0.29,2.51)	0.985
	Comparison	176	4.5		
Enlisted Flyer	Ranch Hand	66	1.5	1.26 (0.08,20.56)	0.999
	Comparison	83	1.2		
Enlisted Groundcrew	Ranch Hand	147	4.8	1.81 (0.60,5.49)	0.441
	Comparison	223	2.7		

b1) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	**Adj. Relative Risk (95% C.I.)**	**p-Value**	**Covariate Remarks[a]**
All	*1.29 (0.61,2.73)*	*0.503*	AGE (p=0.076) PACKYR (p=0.037)
Officer	0.94 (0.32,2.80)	0.913	
Enlisted Flyer	1.40 (0.09,22.86)	0.814	
Enlisted Groundcrew	1.75 (0.57,5.35)	0.325	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-17. (Continued)
Analysis of Double Labelled Cells: CD3 with CD16+56 Cells (cells/mm^3)
(Nonzero Measurements)

a2) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	Group	n	Mean[ab]	Difference of Means (95% C.I.)[c]	p-Value[d]
All	***Ranch Hand***	***353***	***72.2***	***0.4 --***	***0.931***
	Comparison	***467***	***71.7***		
Officer	Ranch Hand	148	74.8	6.6 --	0.449
	Comparison	168	68.2		
Enlisted Flyer	Ranch Hand	65	77.3	12.3 --	0.424
	Comparison	82	65.0		
Enlisted Groundcrew	Ranch Hand	140	64.8	-8.1 --	0.465
	Comparison	217	72.9		

b2) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	Group	n	Adj. Mean[ac]	Difference of Adj. Means (95% C.I.)[c]	p-Value[d]	Covariate Remarks[f]
All	***Ranch Hand***	***350***	***91.5***	***-1.8 --***	0.771	AGE (p<0.001)
	Comparison	***463***	***93.3***			RACE (p<0.001)
Officer	Ranch Hand	148	98.1	4.8--	0.637	CSMOK (p=0.025)
	Comparison	167	93.3			ALC (p=0.053)
Enlisted Flyer	Ranch Hand	63	84.9	-5.0 --	0.720	
	Comparison	82	89.9			
Enlisted Groundcrew	Ranch Hand	139	88.9	-6.9 --	0.475	
	Comparison	214	95.8			

[a] Transformed from the natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[c] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

[d] P-values based on difference of means on natural logarithm scale.

[e] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

[f] Covariates and associated p-values correspond to final model based on all participants with available data.

Note: Analysis based on measurements above 0 cells/mm^3 only.

Table 19-17. (Continued)
Analysis of Double Labelled Cells: CD3 with CD16+56
(Zero vs. Nonzero)

c1) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Zero	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	64	3.1	1.60 (0.95,2.70)	0.070
Medium	67	1.5		
High	72	8.3		

d1) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)[c]			
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
203	****	****	INIT*OCC (p=0.005) PHYACT (p=0.046)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

**** Log_2 (initial dioxin)-by-covariate interaction ($p \leq 0.01$); adjusted relative risk, confidence interval, and p-value not presented; refer to Appendix Table O-2-13 for further analysis of this interaction.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-17. (Continued)
Analysis of Double Labelled Cells: CD3 with CD16+56 Cells (cells/mm³)
(Nonzero Measurements)

c2) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED						
Initial Dioxin Category Summary Statistics				Analysis Results for Log_2 (Initial Dioxin)[b]		
Initial Dioxin	n	Mean[a]	Adj. Mean[ab]	R^2	Slope (Std. Error)[c]	p-Value
Low	62	79.0	81.6	0.438	-0.138 (0.071)	0.055
Medium	66	77.7	81.0			
High	66	60.0	58.3			

d2) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	62	121.1	0.523	-0.129 (0.081)	0.115	OCC (p=0.076) RACE (p=0.066) CSMOK (p=0.022) PACKYR (p=0.035) DRKYR (p=0.006)
Medium	64	122.4				
High	65	94.4				

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

[c] Slope and standard error based on natural logarithm of CD3 with CD16+56 versus $\log_2$ (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

Note: Analysis based on measurements above 0 cells/mm³ only.
Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-17. (Continued)
Analysis of Double Labelled Cells: CD3 with CD16+56
(Zero vs. Nonzero)

e1) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Zero	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	404	3.5		
Background RH	141	2.8	0.79 (0.25,2.47)	0.685
Low RH	95	2.1	0.62 (0.14,2.78)	0.529
High RH	108	6.4	1.92 (0.74,4.96)	0.177
Low plus High RH	203	4.4	1.30 (0.55,3.07)	0.553

f1) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	403			PACKYR (p=0.033)
Background RH	141	0.77 (0.25,2.41)	0.652	
Low RH	95	0.70 (0.15,3.17)	0.642	
High RH	108	1.85 (0.71,4.81)	0.204	
Low plus High RH	203	1.35 (0.57,3.20)	0.501	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin $\leq$ 10 ppt.
Background (Ranch Hand): Current Dioxin $\leq$ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin $\leq$ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-17. (Continued)
Analysis of Double Labelled Cells: CD3 with CD16+56 Cells (cells/mm³)
(Nonzero Measurements)

e2) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED					
Dioxin Category	n	Mean[a]	Adj. Mean[ab]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]
Comparison	390	72.2	72.1		
Background RH	137	77.6	78.8	6.7 --	0.355
Low RH	93	78.9	78.3	6.2 --	0.458
High RH	101	62.4	62.0	-10.1 --	0.158
Low plus High RH	194	69.8	69.3	-2.8 --	0.645

f2) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED					
Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	387	100.9			AGE (p=0.002) RACE (p<0.001) CSMOK (p=0.089) ALC (p=0.004)
Background RH	136	106.0	5.1 --	0.603	
Low RH	93	101.3	0.4 --	0.974	
High RH	99	85.0	-15.9 --	0.103	
Low plus High RH	192	92.5	-8.4 --	0.294	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

[c] Difference of adjusted means after transformation to original scale; confidence interval on difference of adjusted means not presented because analysis was performed on natural logarithm scale.

[d] P-value is based on difference of means on natural logarithm scale.

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

Note: Analysis based on measurements above 0 cells/mm³ only.
RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-17. (Continued)
Analysis of Double Labelled Cells: CD3 with CD16+56
(Zero vs. Nonzero)

g1) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Zero/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	2.6 (116)	2.8 (107)	5.8 (121)	1.53 (1.06,2.22)	0.024
5	2.7 (112)	1.7 (116)	6.9 (116)	1.56 (1.11,2.21)	0.010
6[c]	2.7 (112)	1.7 (116)	6.9 (116)	1.46 (1.01,2.10)	0.042

h1) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	344	****	****	CURR*PHYACT (p=0.004)
5	344	****	****	CURR*PHYACT (p=0.008)
6[d]	344	****	****	CURR*PHYACT (p=0.008)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

**** Log_2 (current dioxin + 1)-by-covariate interaction ($p \leq 0.01$); adjusted relative risk, confidence interval, and p-value not presented; refer to Appendix Table O-2-13 for further analysis of this interaction.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 19-17. (Continued)
Analysis of Double Labelled Cells: CD3 with CD16+56 Cells ($cells/mm^3$) (Nonzero Measurements)

g2) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED

	Current Dioxin Category Mean[ab]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[c]	Low	Medium	High	R^2	Slope (Std. Error)[d]	p-Value
4	83.4 (113)	82.1 (104)	56.6 (114)	0.302	-0.102 (0.041)	0.014
5	85.6 (109)	75.8 (114)	58.9 (108)	0.304	-0.093 (0.035)	0.009
6[e]	82.0 (109)	75.5 (114)	60.6 (108)	0.308	-0.074 (0.038)	0.053

h2) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED

	Current Dioxin Category Adjusted Mean[af]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[c]	Low	Medium	High	R^2	Adj. Slope (Std. Error)[d]	p-Value	Covariate Remarks
4	101.9 (112)	96.9 (104)	71.1 (112)	0.339	-0.086 (0.042)	0.040	AGE (p=0.056) RACE (p=0.038) ALC (p=0.009)
5	106.7 (108)	90.3 (114)	76.3 (106)	0.340	-0.077 (0.036)	0.032	AGE (p=0.052) RACE (p=0.041) ALC (p=0.010)
6[e]	101.6 (108)	88.8 (114)	77.3 (106)	0.343	-0.060 (0.039)	0.122	AGE (p=0.043) RACE (p=0.054) ALC (p=0.010)

[a] Transformed from natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[c] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[d] Slope and standard error based on natural logarithm of CD3 with CD16+56 Cells versus log_2 (current dioxin).

[e] Adjusted for log_2 total lipids.

[f] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

Note: Analysis based on measurements above 0 $cells/mm^3$ only.
Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Based on the nonzero CD3 with CD16+56 cells counts, the Model 1 unadjusted and adjusted analyses were nonsignificant (Table 19-17(a2,b2): $p>0.42$ for all analyses).

The unadjusted Model 2 analysis of the dichotomized CD3 with CD16+56 cell counts revealed a marginally significant positive association with initial dioxin (Table 19-17(c1): $p=0.070$, Est. RR=1.60). The adjusted Model 2 analysis displayed a highly significant interaction between initial dioxin and occupation (Table 19-17(d1): $p=0.005$). Model 2 also was adjusted for the physical activity index. Stratified analyses of the interaction with occupation revealed a significant positive association between initial dioxin and the proportion of zero CD3 with CD16+56 cell counts for the enlisted groundcrew (Appendix Table O-2-13(a): $p=0.048$, Adj. RR=2.30). The percentages of zero CD3 with CD16+56 cell counts for the low, medium, and high initial dioxin categories of enlisted groundcrew were 0.0, 2.8, and 0.2 percent.

The unadjusted Model 2 analysis of the nonzero CD3 with CD16+56 cell counts revealed a marginally significant inverse association with initial dioxin (Table 19-17(c2): $p=0.055$). The mean cell counts, adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, were lowest for Ranch Hands in the high initial dioxin category (low = 81.6 cells/mm^3, medium = 81.0 cells/mm^3, and high = 58.3 cells/mm^3). After adjusting Model 2 for occupation, race, current cigarette smoking, lifetime cigarette smoking history, and lifetime alcohol history, the association between CD3 with CD16+56 cell counts and initial dioxin was nonsignificant (Table 19-17(d2): $p=0.115$). When occupation was removed from the final adjusted model, the association became significant (Appendix Table O-3-13(b): $p=0.004$).

The Model 3 unadjusted and adjusted analyses of the proportion of zero CD3 with CD16+56 cell counts did not find any significant associations with categorized dioxin (Table 19-17(e1,f1): $p>0.17$). The adjusted Model 3 analysis accounted for lifetime cigarette smoking history.

Both the unadjusted and adjusted Model 3 analyses of the nonzero CD3 with CD16+56 cell counts were nonsignificant (Table 19-17(e2,f2): $p>0.10$). Model 3 was adjusted for age, race, current cigarette smoking, and current alcohol use.

The unadjusted analyses of Models 4 through 6 revealed significant positive associations between the proportion of zero CD3 with CD16+56 cell counts and current dioxin (Table 19-17(g1): $p=0.024$, Est. RR=1.53; $p=0.010$, Est. RR=1.56; and $p=0.042$, Est. RR=1.46). The percentages of zero CD3 with CD16+56 cell counts for the low, medium, and high current dioxin categories were 2.6, 2.8, and 5.8 percent for Model 4, and 2.7, 1.7, and 6.9 percent for Models 5 and 6. The adjusted analyses of Models 4 through 6 each exhibited a highly significant current dioxin-by-physical activity index interaction (Table 19-17(h1): $p=0.004$, $p=0.008$, and $p=0.008$ respectively). Stratified analyses of these interactions display highly significant positive associations between the proportion of zero CD3 with CD16+56 cell counts and current dioxin for sedentary Ranch Hands (Appendix Table O-2-13(b-d): $p=0.002$, $p=0.001$, and $p=0.003$ for Models 4, 5, and 6). The percentages of zero CD3 with CD16+56 cell counts for sedentary Ranch Hands in the

low, medium, and high current dioxin categories were 0.0, 2.0, and 7.7 percent for Model 4, and 0.0, 1.9, and 8.1 percent for Models 5 and 6.

The unadjusted analyses of Models 4 through 6 revealed significant and marginally significant inverse associations between the nonzero CD3 with CD16+56 cell counts and current dioxin (Table 19-17(g2): $p=0.014$, $p=0.009$, and $p=0.053$ for Models 4, 5, and 6). The mean CD3 with CD16+56 cell counts decreased with increasing levels of current dioxin (Model 4: low = 83.4, medium = 82.1, and high = 56.6 cells/mm^3; Model 5: low = 85.6, medium = 75.8, and high = 58.9 cells/mm^3; Model 6: low = 82.0, medium = 75.5, and high = 60.6 cells/mm^3). Similarly, the adjusted analysis of Models 4 and 5 revealed significant inverse associations between nonzero CD3 with CD16+56 cell counts (Table 19-17(h2): $p=0.040$ and $p=0.032$ respectively). The adjusted Model 4 means for the low, medium, and high current dioxin categories were 101.9, 96.9, and 71.1 cells/mm^3. Similarly, the Model 5 adjusted means were 106.7, 90.3, and 76.3 cells/mm^3. The adjusted Model 6 analysis was nonsignificant ($p=0.122$). Models 4 through 6 each were adjusted for age, race, and current alcohol use.

Total Lymphocyte Count

The unadjusted and adjusted Model 1 analyses of total lymphocyte count revealed no significant differences between Ranch Hands and Comparisons (Table 19-18(a,b): $p>0.12$ for all contrasts). Occupation and current cigarette smoking were significant covariates in the adjusted model.

The unadjusted Model 2 and Model 3 unadjusted analyses showed no significant associations between dioxin and total lymphocyte count (Table 19-18(c,e): $p>0.28$ for all analyses). A highly significant interaction between initial dioxin and the physical activity index was present in the adjusted analysis of Model 2 (Table 19-18(d): $p=0.009$). A categorized dioxin-by-age interaction was significant in the adjusted analysis of Model 3 (Table 19-18(f): $p=0.046$). Stratified analyses of these interactions are presented in Appendix Table O-2-14. The adjusted Model 3 analysis, after the categorized dioxin-by-age interaction was removed, displayed no significant results (Table 19-18(f): $p>0.50$ for all contrasts). Age and current cigarette smoking were included in the adjusted Model 2 analysis. In Model 3, current cigarette smoking and current alcohol use were retained.

There were no significant associations between current dioxin and total lymphocyte count in the unadjusted and adjusted analyses of Models 4, 5, and 6 (Table 19-18 (g,h): $p>0.56$ for all analyses). Current cigarette smoking was a significant covariate in the adjusted analyses of Models 4, 5, and 6. Current alcohol use also was included in the Model 6 adjusted analysis.

IgA

Analysis of IgA did not reveal a significant difference in means between Ranch Hands and Comparisons in either the unadjusted or adjusted analyses of Model 1 (Table 19-19(a,b):$p>0.52$ for all unadjusted and adjusted analyses). The covariates age, occupation, and current alcohol use were retained for in the final adjusted model.

Table 19-18.
Analysis of TLC (cells/mm^3)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	Group	n	Mean[ab]	Difference of Means (95% C.I.)[c]	p-Value[d]
All	***Ranch Hand***	***367***	***2,059.4***	***9.3 --***	***0.851***
	Comparison	***482***	***2,050.1***		
Officer	Ranch Hand	154	2,002.3	121.2 --	0.129
	Comparison	176	1,881.1		
Enlisted Flyer	Ranch Hand	66	2,002.4	-105.6 --	0.531
	Comparison	83	2,108.0		
Enlisted Groundcrew	Ranch Hand	147	2,175.3	75.3 --	0.373
	Comparison	223	2,100.0		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	Group	n	Adj. Mean[ae]	Difference of Adj. Means (95% C.I.)[c]	p-Value[d]	Covariate Remarks[f]
All	***Ranch Hand***	***367***	***2,063.9***	***20.1 --***	0.672	OCC (p=0.037)
	Comparison	***481***	***2,043.8***			CSMOK (p<0.001)
Officer	Ranch Hand	154	2,021.4	59.5 --	0.413	
	Comparison	176	1,961.9			
Enlisted Flyer	Ranch Hand	66	1,974.4	-134.4 --	0.230	
	Comparison	83	2,108.8			
Enlisted Groundcrew	Ranch Hand	147	2,152.6	48.1 --	0.525	
	Comparison	222	2,104.5			

[a] Transformed from the natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[c] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

[d] P-values based on difference of means on natural logarithm scale.

[e] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

[f] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-18. (Continued)
Analysis of TLC (cells/mm³)

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED						
Initial Dioxin Category Summary Statistics				Analysis Results for Log_2 (Initial Dioxin)[b]		
Initial Dioxin	n	Mean[a]	Adj. Mean[ab]	R^2	Slope (Std. Error)[c]	p-Value
Low	64	1,914.3	1,941.7	0.452	0.024 (0.022)	0.282
Medium	67	2,036.6	2,070.0			
High	72	2,176.2	2,142.0			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	64	****	0.578	****	****	INIT*PHYACT (p=0.009) AGE (p=0.061) CSMOK (p<0. 001)
Medium	67	****				
High	72	****				

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

[c] Slope and standard error based on natural logarithm of TLC versus log_2 (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

**** Log_2 (initial dioxin)-by-covariate interaction ($p \leq 0.01$); adjusted mean, adjusted slope, standard error, and p-value not presented; refer to Appendix Table O-2-14 for further analysis of this interaction.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-18. (Continued)
Analysis of TLC (cells/mm³)

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED					
Dioxin Category	n	Mean[a]	Adj. Mean[ab]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]
Comparison	404	2,022.0	2,021.7		
Background RH	141	2,054.3	2,059.2	37.5 --	0.587
Low RH	95	1,949.3	1,956.9	-64.8 --	0.409
High RH	108	2,073.9	2,065.1	43.4 --	0.568
Low plus High RH	203	2,014.6	2,013.7	-8.0 --	0.894

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED					
Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	400	2,022.4**			DXCAT*AGE (p=0.046) CSMOK (p<0.001) ALC (p=0.139)
Background RH	140	2,066.7**	44.3 --**	0.507**	
Low RH	95	1,998.6**	-23.8 --**	0.757**	
High RH	106	2,034.4**	12.0 --**	0.870**	
Low plus High RH	201	2,017.4**	-5.0 --**	0.931**	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

[c] Difference of adjusted means after transformation to original scale; confidence interval on difference of adjusted means not presented because analysis was performed on natural logarithm scale.

[d] P-value is based on difference of means on natural logarithm scale.

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

** Categorized dioxin-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-14 for further analysis of this interaction.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-18. (Continued)
Analysis of TLC (cells/mm³)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean[ab]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[c]	Low	Medium	High	R^2	Slope (Std. Error)[d]	p-Value
4	2,033.3 (116)	2,002.2 (107)	2,048.6 (121)	0.269	0.005 (0.014)	0.702
5	2,045.9 (112)	1,960.1 (116)	2,087.1 (116)	0.270	0.005 (0.012)	0.657
6[e]	2,070.2 (112)	1,962.9 (116)	2,067.5 (116)	0.274	-0.001 (0.013)	0.957

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[c]	Low	Medium	High	R^2	Adj. Slope (Std. Error)[d]	p-Value	Covariate Remarks
4	2,025.8 (116)	2,035.4 (107)	2,037.8 (121)	0.352	0.005 (0.013)	0.684	CSMOK ($p<0.001$)
5	2,042.2 (112)	1,983.1 (116)	2,079.4 (116)	0.352	0.006 (0.011)	0.566	CSMOK ($p<0.001$)
6[e]	2,064.7 (111)	1,988.3 (116)	2,068.0 (114)	0.361	0.002 (0.012)	0.869	CSMOK ($p<0.001$) ALC ($p=0.148$)

[a] Transformed from natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[c] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[d] Slope and standard error based on natural logarithm of TLC versus log_2 (current dioxin + 1).

[e] Adjusted for log_2 total lipids.

[f] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 19-19.
Analysis of IgA (mg/dl)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Mean[a]**	**Difference of Means (95% C.I.)[b]**	**p-Value[c]**
All	***Ranch Hand***	***936***	***217.2***	***-1.2 --***	***0.787***
	Comparison	***1,264***	***218.4***		
Officer	Ranch Hand	363	211.4	-2.7 --	0.701
	Comparison	492	214.1		
Enlisted Flyer	Ranch Hand	160	214.0	-0.8 --	0.943
	Comparison	200	214.8		
Enlisted Groundcrew	Ranch Hand	413	223.6	0.3 --	0.962
	Comparison	572	223.3		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	**Group**	**n**	**Adj. Mean[a]**	**Difference of Adj. Means (95% C.I.)[b]**	**p-Value[c]**	**Covariate Remarks[d]**
All	***Ranch Hand***	***926***	***215.5***	***-1.5 --***	0.729	AGE ($p<0.001$)
	Comparison	***1,246***	***217.0***			OCC ($p=0.001$)
Officer	Ranch Hand	363	206.4	-4.3 --	0.528	ALC ($p=0.063$)
	Comparison	485	210.7			
Enlisted Flyer	Ranch Hand	157	212.8	0.7 --	0.954	
	Comparison	200	212.1			
Enlisted Groundcrew	Ranch Hand	406	228.4	0.3 --	0.970	
	Comparison	561	228.1			

[a] Transformed from the natural logarithm scale.

[b] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

[c] P-values based on difference of means on natural logarithm scale.

[d] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-19. (Continued)
Analysis of IgA (mg/dl)

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED						
Initial Dioxin Category Summary Statistics				Analysis Results for Log_2 (Initial Dioxin)[b]		
Initial Dioxin	n	Mean[a]	Adj. Mean[ab]	R^2	Slope (Std. Error)[c]	p-Value
Low	171	213.4	213.2	0.010	0.020 (0.016)	0.211
Medium	172	221.8	222.3			
High	168	222.7	222.5			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	171	234.3	0.035	0.032 (0.016)	0.052	AGE (p=0.080) RACE (p=0.001)
Medium	172	249.1				
High	168	253.5				

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Slope and standard error based on natural logarithm of IgA versus $\log_2$ (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-19. (Continued)
Analysis of IgA (mg/dl)

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED					
Dioxin Category	n	Mean[a]	Adj. Mean[ab]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]
Comparison	1,051	220.4	220.4		
Background RH	367	214.6	216.5	-3.9 --	0.529
Low RH	256	216.9	215.6	-4.8 --	0.490
High RH	255	221.6	220.2	-0.2 --	0.987
Low plus High RH	511	219.3	217.8	-2.6 --	0.648

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED					
Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	1,051	228.2**			DXCAT*RACE (p=0.027) AGE (p<0.001) OCC (p=0.009)
Background RH	367	226.4**	-1.8 --**	0.780**	
Low RH	256	221.7**	-6.5 --**	0.365**	
High RH	255	226.2**	-2.0 --**	0.795**	
Low plus High RH	511	224.0**	-4.2 --**	0.453**	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Difference of adjusted means after transformation to original scale; confidence interval on difference of adjusted means not presented because analysis was performed on natural logarithm scale.

[d] P-value is based on difference of means on natural logarithm scale.

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

** Categorized dioxin-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-15 for further analysis of this interaction.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-19. (Continued)
Analysis of IgA (mg/dl)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[b]	Low	Medium	High	R^2	Slope (Std. Error)[c]	p-Value
4	213.1 (289)	217.4 (295)	221.4 (294)	0.002	0.013 (0.011)	0.218
5	213.4 (294)	221.5 (292)	217.1 (292)	0.001	0.007 (0.009)	0.455
6[d]	210.1 (293)	221.3 (292)	220.0 (292)	0.006	0.016 (0.010)	0.099

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[b]	Low	Medium	High	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
4	230.5 (289)	229.3 (295)	232.0 (294)	0.026	0.008 (0.012)	0.530	AGE ($p<0.001$) OCC ($p=0.046$) RACE ($p=0.027$)
5	230.7 (294)	233.0 (292)	225.8 (292)	0.025	0.001 (0.010)	0.945	AGE ($p<0.001$) OCC ($p=0.023$) RACE ($p=0.030$)
6[e]	225.7 (292)	232.0 (292)	229.8 (292)	0.033	0.014 (0.011)	0.202	AGE ($p=0.001$) OCC ($p=0.064$) RACE ($p=0.027$) PACKYR ($p=0.098$)

[a] Transformed from natural logarithm scale.

[b] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for $\log_2$ total lipids.

[c] Slope and standard error based on natural logarithm of IgA versus $\log_2$ (current dioxin + 1).

[d] Adjusted for $\log_2$ total lipids.

[e] Adjusted for $\log_2$ total lipids in addition to covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

The unadjusted analysis of Model 2 did not reveal any significant results (Table 19-19(c): $p=0.211$). The adjusted analysis, however, showed a marginally significant positive association between IgA and initial dioxin (Table 19-19(d): $p=0.052$, Slope=0.032). The adjusted means in the low, medium, and high initial dioxin categories are 234.3 mg/dl, 249.1 mg/dl, and 253.5 mg/dl respectively. Age and race were included in the final adjusted model of Model 2.

The unadjusted analysis of Model 3 did not show a significant relationship between categorized dioxin and IgA (Table 19-19(e): $p \geq 0.49$ for all unadjusted contrasts). However, adjusting for covariates revealed a significant categorized dioxin-by-race interaction (Table 19-19(f): $p=0.027$). Age and occupation also were significant in the final model. Removal of the interaction showed no significant association between categorized dioxin and IgA (Table 19-19(f): $p>0.36$ for all adjusted contrasts). Stratified results of the categorized dioxin-by-race interaction are displayed in Appendix Table O-2-15.

Models 4 and 5 showed no significant relationships between IgA and current dioxin in the unadjusted and adjusted analyses (Table 19-19(g,h): $p>0.21$ for unadjusted and adjusted analyses). Age, occupation, and race were significant in each of the final adjusted models of Models 4 and 5. After excluding occupation from the final model in Model 4, the results became marginally significant (Appendix Table O-3-14(b): $p=0.062$, Slope=0.020). The unadjusted analysis of Model 6 showed a marginally significant association between current dioxin and IgA (Table 19-19(g): $p=0.099$, Slope=0.016). The unadjusted means in the low, medium, and high current dioxin categories were 210.1 mg/dl, 221.3 mg/dl, and 220.0 mg/dl respectively. The adjusted analysis of Model 6 did not reveal a significant relationship between IgA and current dioxin (Table 19-19(h): $p=0.202$). Covariates in the final adjusted model were age, occupation, race, and lifetime cigarette smoking history. After excluding occupation from the final adjusted model of Model 6, a significant positive relationship between IgA and current lipid-adjusted dioxin was revealed (Appendix Table O-3-14(b): $p=0.019$, Slope=0.024).

IgG

The unadjusted analysis of Model 1 displayed a marginally significant difference in mean IgG values between Ranch Hands (1,032.1 mg/dl) and Comparisons (1,051.7 mg/dl) (Table 19-20(a): $p=0.058$). Similarly, the adjusted analysis of Model 1 revealed a marginally significant difference in means between Ranch Hands and Comparisons (Table 19-20(b): $p=0.092$). The adjusted means for Ranch Hands and Comparisons were 1,123.2 mg/dl and 1,141.5 mg/dl. Age, occupation, race, current cigarette smoking, and lifetime cigarette smoking history were significant in the final adjusted model.

The Model 2 unadjusted and adjusted analyses of IgG were nonsignificant (Table 19-20(c,d): $p>0.55$ for unadjusted and adjusted analyses). Occupation, race, current cigarette smoking, and current alcohol use were included in the adjusted analysis. The unadjusted analysis of Model 3 did not reveal a significant relationship between IgG and categorized dioxin (Table 19-20(e): $p>0.14$ for all unadjusted analyses). After adjusting for covariates in Model 3, a significant interaction between categorized dioxin and occupation was revealed (Table 19-20(f): $p=0.024$). Age, race, current cigarette smoking, lifetime cigarette smoking

Table 19-20.
Analysis of IgG (mg/dl)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Mean[a]**	**Difference of Means (95% C.I.)[b]**	**p-Value[c]**
All	***Ranch Hand***	***936***	***1,032.1***	***-19.6 --***	***0.058***
	Comparison	***1,264***	***1,051.7***		
Officer	Ranch Hand	363	1,014.5	-22.1 --	0.157
	Comparison	492	1,036.6		
Enlisted Flyer	Ranch Hand	160	1,003.7	-43.0 --	0.104
	Comparison	200	1,046.7		
Enlisted Groundcrew	Ranch Hand	413	1,059.2	-7.4 --	0.643
	Comparison	572	1,066.6		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	**Group**	**n**	**Adj. Mean[a]**	**Difference of Adj. Means (95% C.I.)[b]**	**p-Value[c]**	**Covariate Remarks[d]**
All	***Ranch Hand***	***935***	***1,123.2***	***-18.3 --***	0.092	AGE (p=0.010)
	Comparison	***1,262***	***1,141.5***			OCC (p=0.001)
Officer	Ranch Hand	362	1,101.2	-23.5 --	0.169	RACE (p<0.001)
	Comparison	492	1,124.7			CSMOK (p<0.001)
Enlisted Flyer	Ranch Hand	160	1,100.6	-41.1 --	0.119	PACKYR (p=0.029)
	Comparison	200	1,141.7			
Enlisted Groundcrew	Ranch Hand	413	1,160.6	-4.8 --	0.770	
	Comparison	570	1,165.4			

[a] Transformed from the natural logarithm scale.

[b] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

[c] P-values based on difference of means on natural logarithm scale.

[d] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-20. (Continued)
Analysis of IgG (mg/dl)

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED						
Initial Dioxin Category Summary Statistics				Analysis Results for Log_2 (Initial Dioxin)[b]		
Initial Dioxin	n	Mean[a]	Adj. Mean[ab]	R^2	Slope (Std. Error)[c]	p-Value
Low	171	1,035.4	1,035.2	0.001	0.005 (0.008)	0.551
Medium	172	1,045.2	1,045.3			
High	168	1,028.3	1,028.3			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	169	1,134.1	0.109	-0.001 (0.009)	0.943	OCC (p=0.057) RACE (p<0.001) CSMOK (p=0.002) ALC (p=0.015)
Medium	169	1,141.3				
High	166	1,101.3				

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Slope and standard error based on natural logarithm of IgG versus $\log_2$ (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-20. (Continued)
Analysis of IgG (mg/dl)

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED					
Dioxin Category	n	Mean[a]	Adj. Mean[ab]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]
Comparison	1,051	1,051.8	1,051.7		
Background RH	367	1,026.8	1,030.4	-21.3 --	0.140
Low RH	256	1,036.4	1,035.0	-16.8 --	0.310
High RH	255	1,036.2	1,033.0	-18.7 --	0.258
Low plus High RH	511	1,036.3	1,034.0	-17.7 --	0.165

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED					
Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	1,035	1,138.7**			DXCAT*OCC (p=0.024) AGE (p=0.097) RACE (p<0.001) CSMOK (p<0.001) PACKYR (p=0.143) ALC (p=0.123)
Background RH	364	1,126.9**	-11.8 --**	0.451**	
Low RH	253	1,111.2**	-27.5 --**	0.112**	
High RH	251	1,115.1**	-23.6 --**	0.189**	
Low plus High RH	504	1,113.1**	-25.6 --**	0.060**	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Difference of adjusted means after transformation to original scale; confidence interval on difference of adjusted means not presented because analysis was performed on natural logarithm scale.

[d] P-value is based on difference of means on natural logarithm scale.

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

** Categorized dioxin-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-16 for further analysis of this interaction.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-20. (Continued)
Analysis of IgG (mg/dl)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[b]	Low	Medium	High	R^2	Slope (Std. Error)[c]	p-Value
4	1,027.1 (289)	1,020.9 (295)	1,049.1 (294)	0.001	0.004 (0.005)	0.508
5	1,031.2 (294)	1,028.1 (292)	1,037.7 (292)	<0.001	-0.001 (0.005)	0.892
6[d]	1,018.9 (293)	1,027.1 (292)	1,051.2 (292)	0.012	0.005 (0.005)	0.290

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[b]	Low	Medium	High	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
4	1,133.1 (288)	1,114.0 (292)	1,135.1 (289)	0.085	-0.003 (0.006)	0.598	OCC (p=0.038) RACE (p<0.001) CSMOK (p<0.001) ALC (p=0.021)
5	1,137.2 (292)	1,119.5 (290)	1,121.2 (287)	0.086	-0.007 (0.005)	0.206	OCC (p=0.018) RACE (p<0.001) CSMOK (p<0.001) ALC (p=0.024)
6[e]	1,123.7 (291)	1,115.8 (290)	1,129.7 (287)	0.091	-0.002 (0.006)	0.714	OCC (p=0.030) RACE (p<0.001) CSMOK (p<0.001) ALC (p=0.033)

[a] Transformed from natural logarithm scale.

[b] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[c] Slope and standard error based on natural logarithm of IgG versus log_2 (current dioxin + 1).

[d] Adjusted for log_2 total lipids.

[e] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

history, and current alcohol use also were retained in the final adjusted model. Removal of the interaction exhibited a significant difference in means between the low plus high Ranch Hand category (1,113.1 mg/dl) and the Comparisons (1,138.7 mg/dl) (Table 19-20(f): $p=0.060$). After excluding occupation from the final model, this contrast became nonsignificant (Appendix Table O-3-15(b): $p=0.104$). Additionally, the contrast between low Ranch Hands and Comparisons became marginally significant after occupation was removed from the final model: $p=0.096$).

The unadjusted and adjusted analysis of Models 4 through 6 did not reveal any significant associations between current dioxin and IgG (Table 19-20(g,h): $p>0.20$ for all unadjusted and adjusted analyses). Occupation, race, current cigarette smoking, and current alcohol use were significant in each of the final adjusted models.

IgM

The Model 1 unadjusted analyses of IgM did not reveal any significant associations between Ranch Hands and Comparisons (Table 19-21(a): $p>0.14$). The adjusted analyses revealed a significant group-by-race interaction and a group-by-physical activity index interaction (Table 19-21(b): $p=0.034$ and $p=0.005$ respectively). Removal of these interactions did not reveal a significant difference in mean IgM values between Ranch Hands and Comparisons (Table 19-21(b): $p>0.12$ for adjusted analyses). Age and current alcohol also were significant in the final adjusted model. Stratified tables of the interactions are displayed in Appendix Table O-2-17.

The Model 2 unadjusted and adjusted analyses did not reveal any significant associations between initial dioxin and IgM (Table 19-21(c,d): $p>0.14$ for unadjusted and adjusted analysis). Age, race, occupation, and the physical activity index were included in the final adjusted model. The unadjusted analysis of Model 3 did not reveal a significant relationship between categorized dioxin and IgM (Table 19-21(e): $p>0.58$). Adjusting for covariates in Model 3 revealed a highly significant interaction between categorized dioxin and physical activity index (Table 19-21(f): $p=0.001$). Stratified results of this interaction are shown in Appendix Table O-2-17. Very active Ranch Hands had significantly higher IgM values than Comparisons, while sedentary and moderately active Ranch Hands generally had slightly lower IgM values than Comparisons. Age, race, and current alcohol use also were significant in the final adjusted model.

The unadjusted analysis of IgM for Models 4 through 6 did not reveal any significant associations with current dioxin (Table 19-21(g): $p>0.69$). The adjusted analysis of Model 4 revealed a significant current dioxin-by-current alcohol use interaction (Table 19-21(h): $p=0.033$). Age, race, and the physical activity index also were significant in the final model. Removal of the interaction did not reveal any significant findings. Stratified results of the current dioxin-by-current alcohol use interaction are presented in Appendix Table O-2-17. Models 5 and 6 did not reveal any significant results in the adjusted analysis (Table 19-21(h): $p>0.68$). Age, race, current alcohol use, and the physical activity index were significant in Models 5 and 6.

Table 19-21.
Analysis of IgM (mg/dl)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	Group	n	Mean[a]	Difference of Means (95% C.I.)[b]	p-Value[c]
All	***Ranch Hand***	***936***	***103.9***	***-1.6 --***	***0.498***
	Comparison	***1,264***	***105.5***		
Officer	Ranch Hand	363	104.3	0.9 --	0.825
	Comparison	492	103.4		
Enlisted Flyer	Ranch Hand	160	100.3	-9.2 --	0.141
	Comparison	200	109.5		
Enlisted Groundcrew	Ranch Hand	413	104.9	-1.2 --	0.748
	Comparison	572	106.1		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	Group	n	Adj. Mean[a]	Difference of Adj. Means (95% C.I.)[b]	p-Value[c]	Covariate Remarks[d]
All	***Ranch Hand***	***926***	***97.0*****	***-1.3 --*****	0.579**	GROUP*RACE (p=0.034)
	Comparison	***1,246***	***98.3*****			GROUP*PHYACT (p=0.005)
Officer	Ranch Hand	363	98.1**	0.6 --**	0.868**	AGE (p<0.001)
	Comparison	485	97.5**			ALC (p=0.019)
Enlisted Flyer	Ranch Hand	157	94.2**	-8.8 --**	0.127**	
	Comparison	200	103.0**			
Enlisted Groundcrew	Ranch Hand	406	97.2**	-0.2 --**	0.950**	
	Comparison	561	97.4**			

[a] Transformed from the natural logarithm scale.

[b] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

[c] P-values based on difference of means on natural logarithm scale.

[d] Covariates and associated p-values correspond to final model based on all participants with available data.

** Group-by-covariate interactions ($p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of these interactions; refer to Appendix Table O-2-17 for further analysis of these interactions.

Table 19-21. (Continued)
Analysis of IgM (mg/dl)

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED						
Initial Dioxin Category Summary Statistics				Analysis Results for Log_2 (Initial Dioxin)[b]		
Initial Dioxin	n	Mean[a]	Adj. Mean[ab]	R^2	Slope (Std. Error)[c]	p-Value
Low	171	100.1	99.8	0.004	0.023 (0.019)	0.230
Medium	172	99.4	99.1			
High	168	107.7	108.2			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	171	93.7	0.057	0.032 (0.022)	0.145	AGE (p=0.021) RACE (p=0.089) OCC (p=0.055) PHYACT (p=0.002)
Medium	172	96.0				
High	168	104.7				

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Slope and standard error based on natural logarithm of IgM versus $\log_2$ (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-21. (Continued)
Analysis of IgM (mg/dl)

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED					
Dioxin Category	n	Mean[a]	Adj. Mean[ab]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]
Comparison	1,051	104.8	104.8		
Background RH	367	106.7	105.4	0.6 --	0.863
Low RH	256	102.0	102.7	-2.1 --	0.610
High RH	255	102.5	103.4	-1.4 --	0.731
Low plus High RH	511	102.3	103.1	-1.7 --	0.581

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED					
Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	1,035	****			DXCAT*PHYACT (p=0.001) AGE (p=0.015) RACE (p=0.002) ALC (p=0.023)
Background RH	365	****	****	****	
Low RH	253	****	****	****	
High RH	251	****	****	****	
Low plus High RH	504	****	****	****	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Difference of adjusted means after transformation to original scale; confidence interval on difference of adjusted means not presented because analysis was performed on natural logarithm scale.

[d] P-value is based on difference of means on natural logarithm scale.

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

**** Categorized dioxin-by-covariate interaction ($p \leq 0.01$); adjusted mean, difference of adjusted means, and p-value not presented; refer to Appendix Table O-2-17 for further analysis of this interaction.

Table 19-21. (Continued)
Analysis of IgM (mg/dl)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[b]	Low	Medium	High	R^2	Slope (Std. Error)[c]	p-Value
4	105.8 (289)	104.8 (295)	101.7 (294)	<0.001	0.001 (0.013)	0.914
5	105.3 (294)	105.6 (292)	101.4 (292)	<0.001	-0.002 (0.011)	0.825
6[d]	104.0 (293)	105.4 (292)	103.1 (292)	0.005	0.005 (0.012)	0.698

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[b]	Low	Medium	High	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
4	95.2** (288)	96.5** (292)	91.4** (289)	0.038	-0.001 (0.013)**	0.954**	CURR*ALC (p=0.033) AGE (p=0.011) RACE (p=0.001) PHYACT (p=0.016)
5	94.7 (292)	96.9 (290)	91.0 (287)	0.033	-0.005 (0.011)	0.685	AGE (p=0.009) RACE (p=0.001) ALC (p=0.041) PHYACT (p=0.015)
6[e]	92.7 (291)	96.2 (290)	92.3 (287)	0.039	0.004 (0.012)	0.761	AGE (p=0.019) RACE (p=0.001) ALC (p=0.027) PHYACT (p=0.016)

[a] Transformed from natural logarithm scale.

[b] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[c] Slope and standard error based on natural logarithm of IgM versus log_2 (current dioxin + 1).

[d] Adjusted for log_2 total lipids.

[e] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

** Log_2 (current dioxin + 1)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-17 for further analysis of this interaction.

Lupus Panel: Antinuclear Antibody (ANA)

The Model 1 unadjusted analysis of the antinuclear antibody (ANA) revealed a marginally significant difference between Ranch Hands and Comparisons (Table 19-22(a): $p=0.092$, Est. RR=0.81). The analysis of ANA yielded positive results for 13.7 percent of Ranch Hands and 16.4 percent of Comparisons. Stratifying by occupation also revealed a marginally significant difference between Ranch Hands and Comparisons in the enlisted groundcrew category (Table 19-22(a): $p=0.073$, Est. RR=0.69). Within the enlisted groundcrew category, 10.9 percent of Ranch Hands and 15.0 percent of Comparisons yielded positive ANA results. Similar to the unadjusted analysis, the Model 1 adjusted analysis revealed a marginally significant difference between Ranch Hands and Comparisons overall and for the enlisted groundcrew (Table 19-22(b): $p=0.067$, Adj. RR=0.80 and $p=0.058$, Adj. RR=0.069 respectively). Age was significant in the final adjusted model.

Model 2 did not display a significant association between initial dioxin and ANA (Table 19-22(c,d): $p>0.59$ for both the unadjusted and adjusted analyses). Age, race, and lifetime alcohol history were significant in the final adjusted model. In Model 3, the unadjusted analysis exhibited a significantly lower percentage of positive ANA results in the high Ranch Hand category (11.4%) and low plus high Ranch Hand combined category (13.1%) than in Comparisons (17.1%) (Table 19-22(e): $p=0.030$, Est. RR=0.63 and 0.047, Est. RR=0.73, respectively). Adjusting for covariates in Model 3 revealed a highly significant categorized dioxin-by-lifetime alcohol history interaction (Table 19-22(f): $p=0.002$). Age also was significant in the final adjusted model. Stratified results of the interaction between lifetime alcohol history and categorized dioxin are presented in Appendix Table O-2-18.

The unadjusted analyses of Models 4 and 5 did not reveal any significant relationships between current dioxin and ANA (Table 19-22(g): $p>0.13$). The unadjusted analysis of Model 6 revealed a marginally significant inverse relationship between ANA and current dioxin (Table 19-22(g): $p=0.099$, Est. RR=0.90). Adjusting for covariates in Models 4 through 6 revealed significant current dioxin-by-race and current dioxin-by-lifetime alcohol history interactions in each model (Table 19-22(h): Model 4, $p=0.023$ and $p=0.002$; Model 5, $p=0.014$ and $p=0.003$; Model 6, $p=0.016$ and $p=0.003$). Age also was significant in the final adjusted model of Models 4 through 6. Removal of the interactions did not reveal any significant associations between current dioxin and ANA. Stratified results of the current dioxin-by-race and current dioxin-by-lifetime alcohol history interactions for Models 4, 5, and 6 are presented in Appendix Table O-2-18.

Lupus Panel: Thyroid Microsomal Antibody

Model 1 revealed a marginally significant overall difference between Ranch Hands and Comparisons in the unadjusted analysis of the thyroid microsomal antibody (Table 19-23(a): $p=0.054$, Est. RR=1.61). The results were positive for 4.4 percent of Ranch Hands and 2.8 percent of Comparisons. Adjusting for covariates in Model 1 revealed three highly significant interactions: group-by-current cigarette smoking, group-by-current alcohol use, and group-by-lifetime alcohol history (Table 19-23(b): $p=0.001$, $p=0.002$, and $p<0.001$ respectively). The physical activity index also was included in the final adjusted model. For further investigation, stratified analyses were performed on each interaction. These results

Table 19-22.
Analysis of Lupus Panel: Antinuclear Antibody (ANA)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED

Occupational Category	Group	n	Percent Present	Est. Relative Risk (95% C.I.)	p-Value
All	***Ranch Hand***	***936***	***13.7***	***0.81 (0.64,1.03)***	***0.092***
	Comparison	***1,264***	***16.4***		
Officer	Ranch Hand	363	15.7	0.86 (0.59,1.23)	0.454
	Comparison	492	17.9		
Enlisted Flyer	Ranch Hand	160	16.3	0.98 (0.56,1.72)	0.999
	Comparison	200	16.5		
Enlisted Groundcrew	Ranch Hand	413	10.9	0.69 (0.47,1.02)	0.073
	Comparison	572	15.0		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED

Occupational Category	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks[a]
All	***0.80 (0.63,1.02)***	***0.067***	AGE ($p<0.001$)
Officer	0.84 (0.59,1.22)	0.365	
Enlisted Flyer	0.97 (0.55,1.71)	0.921	
Enlisted Groundcrew	0.69 (0.47,1.01)	0.058	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-22. (Continued)
Analysis of Lupus Panel: Antinuclear Antibody (ANA)

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Present	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	171	16.4	0.95 (0.77,1.16)	0.599
Medium	172	10.5		
High	168	12.5		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)[c]			
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
498	1.02 (0.82,1.27)	0.865	AGE (p=0.005) RACE (p=0.149) DRKYR (p=0.002)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-22. (Continued)
Analysis of Lupus Panel: Antinuclear Antibody (ANA)

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Present	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,051	17.1		
Background RH	367	15.5	0.88 (0.63,1.22)	0.445
Low RH	256	14.8	0.84 (0.58,1.23)	0.378
High RH	255	11.4	0.63 (0.41,0.96)	0.030
Low plus High RH	511	13.1	0.73 (0.54,1.00)	0.047

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	1,033			DXCAT*DRKYR ($p=0.002$) AGE ($p<0.001$)
Background RH	361	****	****	
Low RH	250	****	****	
High RH	248	****	****	
Low plus High RH	498	****	****	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

**** Categorized dioxin-by-covariate interaction ($p \leq 0.01$); adjusted relative risk, confidence interval, and p-value not presented; refer to Appendix Table O-2-18 for further analysis of this interaction.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-22. (Continued)
Analysis of Lupus Panel: Antinuclear Antibody (ANA)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Present/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	16.6 (289)	14.9 (295)	10.9 (294)	0.90 (0.79,1.03)	0.137
5	15.3 (294)	16.1 (292)	11.0 (292)	0.93 (0.84,1.04)	0.233
6[c]	15.4 (293)	16.1 (292)	11.0 (292)	0.90 (0.80,1.02)	0.099

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	859	0.95 (0.82,1.09)**	0.431**	CURR*RACE (p=0.023) CURR*DRKYR (p=0.002) AGE (p<0.001)
5	859	0.97 (0.86,1.09)**	0.554**	CURR*RACE (p=0.014) CURR*DRKYR (p=0.003) AGE (p<0.001)
6[d]	858	0.94 (0.83,1.07)**	0.341**	CURR*RACE (p=0.016) CURR*DRKYR (p=0.003) AGE (p<0.001)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for $\log_2$ total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for $\log_2$ total lipids.

[d] Adjusted for $\log_2$ total lipids in addition to covariates specified under "Covariate Remarks" column.

** Log_2 (current dioxin + 1)-by-covariate interactions ($p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of these interactions; refer to Appendix Table O-2-18 for further analysis of these interactions.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 19-23.
Analysis of Lupus Panel: Thyroid Microsomal Antibody

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	Group	n	Percent Present	Est. Relative Risk (95% C.I.)	p-Value
All	*Ranch Hand*	*936*	*4.4*	*1.61 (1.02,2.55)*	*0.054*
	Comparison	*1,264*	*2.8*		
Officer	Ranch Hand	363	4.1	1.20 (0.59,2.45)	0.739
	Comparison	492	3.5		
Enlisted Flyer	Ranch Hand	160	5.0	3.46 (0.90,13.25)	0.108
	Comparison	200	1.5		
Enlisted Groundcrew	Ranch Hand	413	4.4	1.69 (0.84,3.40)	0.189
	Comparison	572	2.6		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks[a]
All	****	****	GROUP*CSMOK (p=0.001) GROUP*ALC (p=0.002) GROUP*DRKYR (p<0.001) PHYACT (p=0.088)
Officer	****	****	
Enlisted Flyer	****	****	
Enlisted Groundcrew	****	****	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

**** Group-by-covariate interactions (p≤0.01); adjusted relative risk, confidence interval, and p-value not presented; refer to Appendix Table O-2-19 for further analysis of these interactions.

Table 19-23. (Continued)
Analysis of Lupus Panel: Thyroid Microsomal Antibody

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Present	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	171	6.4	0.91 (0.67,1.24)	0.559
Medium	172	4.1		
High	168	5.4		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)[c]			
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
498	0.82 (0.59,1.14)**	0.228**	INIT*DRKYR (p=0.014) INIT*CSMOK (p=0.025) PACKYR (p=0.031) ALC (p<0.001) PHYACT (P=0.034)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

** Log_2 (initial dioxin)-by-covariate interactions ($0.01 < p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of these interactions; refer to Appendix Table O-2-19 for further analysis of these interactions.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-23. (Continued)
Analysis of Lupus Panel: Thyroid Microsomal Antibody

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Present	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,051	2.8		
Background RH	367	3.5	1.31 (0.67,2.56)	0.431
Low RH	256	5.9	2.14 (1.13,4.07)	0.020
High RH	255	4.7	1.74 (0.87,3.47)	0.119
Low plus High RH	511	5.3	1.94 (1.13,3.33)	0.016

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	1,033			DXCAT*CSMOK (p=0.001) DXCAT*ALC (p<0.001) DXCAT*DRKYR (p<0.001) AGE (p=0.120)
Background RH	361	****	****	
Low RH	250	****	****	
High RH	248	****	****	
Low plus High RH	498	****	****	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

**** Categorized dioxin-by-covariate interactions ($p \leq 0.01$); adjusted relative risk, confidence interval, and p-value not presented; refer to Appendix Table O-2-19 for further analysis of these interactions.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-23. (Continued)
Analysis of Lupus Panel: Thyroid Microsomal Antibody

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Present/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	3.5 (289)	5.8 (295)	4.4 (294)	1.08 (0.87,1.34)	0.478
5	3.1 (294)	5.8 (292)	4.8 (292)	1.10 (0.91,1.32)	0.327
6[c]	3.1 (293)	5.8 (292)	4.8 (292)	1.06 (0.86,1.29)	0.587

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	868	1.09 (0.88,1.34)**	0.449**	CURR*ALC (p=0.044) PACKYR (p=0.009)
5	868	1.10 (0.92,1.32)	0.302	PACKYR (p=0.009) ALC (p=0.014)
6[d]	867	1.07 (0.88,1.30)	0.507	PACKYR (p=0.013) ALC (p=0.014)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

** Log_2 (current dioxin + 1)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-19 for further analysis of this interaction.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

are displayed in Appendix Table O-2-19. Ranch Hands with more than 40 drink-years had significantly higher percentage of thyroid microsomal antibody than Comparisons overall and in each of the occupational categories.

The unadjusted analysis of Model 2 did not reveal a significant association between the thyroid microsomal antibody and initial dioxin (Table 19-23(c): p=0.559). The adjusted analysis revealed significant initial dioxin-by-lifetime alcohol history and initial dioxin-by-current cigarette smoking interactions (Table 19-23(d): p=0.014 and p=0.025). Lifetime cigarette smoking history, current alcohol use, and the physical activity index also were significant in the final adjusted model. Removal of the interactions did not reveal a significant association between initial dioxin and the presence of the thyroid microsomal antibodies (p=0.228). Stratified results of each interaction are presented in Appendix Table O-2-19.

In Model 3, the unadjusted analysis exhibited a significantly higher percentage of positive thyroid microsomal antibody test results in the low Ranch Hand category (5.9%) and the low plus high Ranch Hand category (5.3%) than in the Comparison group (2.8%) (Table 19-23(e): p=0.020, Est. RR=2.14 and p=0.016, Est. RR=1.94 respectively). Adjusting for covariates in Model 3 revealed three highly significant interactions with categorized dioxin: categorized dioxin-by-current cigarette smoking, categorized dioxin-by-current alcohol use, and categorized dioxin-by-lifetime alcohol history (Table 19-23(f): p=0.001, p<0.001, and p<0.001 respectively). Age also was retained in the final adjusted model. Stratified results of each interaction are shown in Appendix Table O-2-19. Ranch Hands who were current or former smokers, light current drinkers (0-1 drink/day), and heavy lifetime drinkers (>40 drink-years) had higher percentages of thyroid microsomal antibodies present than Comparisons.

The unadjusted analyses of Models 4 through 6 did not show any significant relationships between current dioxin and thyroid microsomal antibodies (Table 19-23(g): p>0.32 for unadjusted analyses). Adjusting for covariates in Model 4 revealed a significant current dioxin-by-current alcohol use interaction (Table 19-23(h): p=0.044). Lifetime smoking history also was significant in the final adjusted model. Removal of the interaction did not reveal a significant association between current dioxin and the presence of thyroid microsomal antibodies. Stratified results of the interaction in Model 4 are presented in Appendix Table O-2-19. The adjusted analyses of Model 5 and 6 did not display any significant results (Table 19-23(h): p>0.30 for adjusted analyses).

Lupus Panel: MSK Smooth Muscle Antibody

The analysis of mouse stomach kidney (MSK) smooth muscle antibody in Model 1 did not show any significant results (Table 19-24(a,b): p>0.31 for unadjusted and adjusted analyses). Age, race, and occupation were accounted for in the final adjusted model.

In Model 2, the unadjusted and adjusted analyses revealed significant inverse relationships between MSK smooth muscle antibodies and initial dioxin (Table 19-24(c,d): p=0.035, Est. RR=0.60 and p=0.022, Adj. RR=0.57). The percentage of participants testing positive for the smooth muscle antibody in the low, medium, and high initial dioxin

Table 19-24.
Analysis of Lupus Panel: MSK Smooth Muscle Antibody

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Percent Present**	**Est. Relative Risk (95% C.I.)**	**p-Value**
All	***Ranch Hand***	***936***	***3.0***	***0.94 (0.58,1.54)***	***0.914***
	Comparison	***1,264***	***3.2***		
Officer	Ranch Hand	363	4.7	1.29 (0.66,2.55)	0.567
	Comparison	492	3.7		
Enlisted Flyer	Ranch Hand	160	1.9	0.75 (0.18,3.17)	0.968
	Comparison	200	2.5		
Enlisted Groundcrew	Ranch Hand	413	1.9	0.65 (0.28,1.51)	0.416
	Comparison	572	3.0		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	**Adj. Relative Risk (95% C.I.)**	**p-Value**	**Covariate Remarks[a]**
All	***0.94 (0.58,1.54)***	***0.805***	AGE (p=0.139) RACE (p=0.060) OCC (p=0.150)
Officer	1.28 (0.65,2.51)	0.481	
Enlisted Flyer	0.75 (0.18,3.20)	0.700	
Enlisted Groundcrew	0.64 (0.28,1.51)	0.312	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-24.
Analysis of Lupus Panel: MSK Smooth Muscle Antibody

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Present	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	171	3.5	0.60 (0.36,1.00)	0.035
Medium	172	3.5		
High	168	1.2		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)[c]			
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
511	0.57 (0.33,0.97)	0.022	PHYACT (p=0.015)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-24. (Continued)
Analysis of Lupus Panel: MSK Smooth Muscle Antibody

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Present	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,051	3.1		
Background RH	367	3.8	1.32 (0.69,2.51)	0.405
Low RH	256	4.3	1.37 (0.68,2.75)	0.383
High RH	255	1.2	0.34 (0.10,1.11)	0.073
Low plus High RH	511	2.7	0.83 (0.44,1.57)	0.563

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	1,051			AGE (p=0.048) RACE (p=0.140)
Background RH	367	1.27 (0.67,2.43)	0.467	
Low RH	256	1.27 (0.63,2.58)	0.503	
High RH	255	0.37 (0.11,1.23)	0.105	
Low plus High RH	511	0.84 (0.44,1.60)	0.594	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-24. (Continued)
Analysis of Lupus Panel: MSK Smooth Muscle Antibody

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Present/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	3.8 (289)	4.1 (295)	1.7 (294)	0.78 (0.59,1.03)	0.070
5	3.7 (294)	3.8 (292)	2.1 (292)	0.85 (0.68,1.05)	0.143
6[c]	3.8 (293)	3.8 (292)	2.1 (292)	0.81 (0.64,1.02)	0.082

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	878	0.80 (0.60,1.07)	0.131	AGE (p=0.097)
5	878	0.87 (0.69,1.09)	0.232	AGE (p=0.081)
6[d]	877	0.83 (0.65,1.06)	0.151	AGE (p=0.096)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = $\leq$ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = $\leq$ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

categories were 3.5 percent, 3.5 percent, and 1.2 percent. The physical activity index was significant in the final adjusted model.

The unadjusted analysis of Model 3 revealed that the percentage of participants testing positive was marginally significantly lower for MSK smooth muscle antibodies in the high Ranch Hand category (1.2%) than in the Comparison group (3.1%) (Table 19-24(e): p=0.073, Est. RR=0.34). The results of the adjusted Model 3 analysis were nonsignificant. Age and race were covariates included in the final adjusted model.

The unadjusted analyses of Models 4 and 6 displayed marginally significant inverse associations between the smooth muscle antibody and current dioxin (Table 19-24(g): p=0.070, Est. RR=0.78; p=0.082, Est. RR=0.81). The percentage of participants testing positive for the smooth muscle antibody in the low, medium, and high categories were 3.8, 4.1, and 1.7 percent for Model 4 and 3.8, 3.8, and 2.1 percent for Model 6. The unadjusted analysis of Model 5 was nonsignificant (p=0.143). The adjusted analyses of Models 4 through 6 did not reveal any significant associations between current dioxin and smooth muscle antibody (Table 19-24(h): p>0.13 for adjusted analyses). Age was retained in each of the final adjusted models for Models 4 through 6.

Lupus Panel: MSK Mitochondrial Antibody

Due to a sparse number of abnormal findings, the adjusted analyses for Models 1 through 6 were not performed.

The unadjusted Model 1 analysis did not reveal any significant differences between Ranch Hands and Comparisons in the presence of MSK mitochondrial antibodies (Table 19-25(a): p>0.62). Because only one Ranch Hand (in the low initial dioxin category) had an MSK mitochondrial antibody present, no unadjusted Model 2 analysis was performed. The unadjusted analyses of Models 3 through 6 did not exhibit any significant associations between the presence of MSK mitochondrial antibodies and categorized dioxin or current dioxin (Table 19-25(e,g): p>0.11 for all analyses).

Lupus Panel: MSK Parietal Antibody

The unadjusted analysis of the parietal antibody did not detect a significant difference between Ranch Hands and Comparisons in Model 1 (Table 19-26(a): p>0.26 for unadjusted analysis). The adjusted analysis of Model 1 revealed a significant group-by-race interaction (Table 19-26(b): p=0.014). Age, current cigarette smoking, and current alcohol use also were included in the final adjusted model. Removal of the group-by-race interaction in Model 1 revealed a marginally significant difference between Ranch Hands and Comparisons within the officer category (Table 19-26(b): p=0.084, Est. RR=1.87). Stratified analyses of the interaction are shown in Appendix Table O-2-20.

Models 2 and 3 did not reveal any significant associations between initial dioxin and the parietal antibody test in the unadjusted and adjusted analyses (Table 19-26(c-f): p>0.22). No covariates were significant in the Model 2 adjusted analysis. Age, current cigarette smoking, and current alcohol use were retained in the final adjusted model for Model 3.

Table 19-25.
Analysis of MSK Mitochondrial Antibody

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Percent Present**	**Est. Relative Risk (95% C.I.)**	**p-Value**
All	***Ranch Hand***	***936***	***0.2***	***0.90 (0.15,5.40)***	***0.999***
	Comparison	***1,264***	***0.2***		
Officer	Ranch Hand	363	0.6	2.72 (0.25,30.12)	0.791
	Comparison	493	0.2		
Enlisted Flyer	Ranch Hand	160	0.0	--	--
	Comparison	200	0.0		
Enlisted Groundcrew	Ranch Hand	413	0.0	0.28 (0.01,5.76)	0.627
	Comparison	572	0.3		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	**Adj. Relative Risk (95% C.I.)**	**p-Value**	**Covariate Remarks**
All	--	--	
Officer	--	--	
Enlisted Flyer	--	--	
Enlisted Groundcrew	--	--	

--: Adjusted analysis not performed due to the sparse number of abnormalities.

Table 19-25. (Continued)
Analysis of MSK Mitochondrial Antibody

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Present	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	171	0.6	--	--
Medium	172	0.0		
High	168	0.0		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)			
n	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
--	--	--	

[a] Adjusted for percent body fat at the time of duty and change in percent body fat from the time of duty to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

--: Adjusted analysis not performed due to the sparse number of abnormalities.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-25. (Continued)
Analysis of MSK Mitochondrial Antibody

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	**n**	**Percent Present**	**Est. Relative Risk (95% C.I.)[ab]**	**p-Value**
Comparison	1,051	0.3		
Background RH	367	0.3	1.41 (0.14,14.30)	0.770
Low RH	256	0.4	1.04 (0.10,10.50)	0.971
High RH	255	0.0	--	--
Low plus High RH	511	0.2	0.49 (0.05,5.04)	0.545

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	**n**	**Adj. Relative Risk (95% C.I.)**	**p-Value**	**Covariate Remarks**
Comparison	--			
Background RH	--	--	--	
Low RH	--	--	--	
High RH	--	--	--	
Low plus High RH	--	--	--	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty and change in percent body fat from the time of duty to the date of the blood draw for dioxin.

--: Adjusted analysis not performed due to the sparse number of abnormalities.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-25. (Continued)
Analysis of MSK Mitochondrial Antibody

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Present/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	0.3 (289)	0.3 (295)	0.0 (294)	0.44 (0.15,1.26)	0.126
5	0.7 (294)	0.0 (292)	0.0 (292)	0.58 (0.32,1.04)	0.114
6[c]	0.7 (293)	0.0 (292)	0.0 (292)	0.63 (0.31,1.26)	0.243

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	--	--	--	
5	--	--	--	
6[c]	--	--	--	

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

--: Adjusted analysis not performed due to the sparse number of abnormalities.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 19-26.
Analysis of Lupus Panel: MSK Parietal Antibody

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	Group	n	Percent Present	Est. Relative Risk (95% C.I.)	p-Value
All	*Ranch Hand*	*936*	*2.4*	*0.90 (0.52,1.55)*	*0.804*
	Comparison	*1,264*	*2.6*		
Officer	Ranch Hand	363	3.0	1.51 (0.63,3.59)	0.479
	Comparison	492	2.0		
Enlisted Flyer	Ranch Hand	160	1.9	0.94 (0.21,4.25)	0.999
	Comparison	200	2.0		
Enlisted Groundcrew	Ranch Hand	413	1.9	0.58 (0.25,1.33)	0.265
	Comparison	572	3.3		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks[a]
All	*0.87 (0.50,1.51)***	*0.618***	GROUP*RACE (p=0.014) AGE (p=0.105) CSMOK (p=0.085) ALC (p=0.031)
Officer	1.87 (0.92,3.80)**	0.084**	
Enlisted Flyer	1.14 (0.36,3.62)**	0.828**	
Enlisted Groundcrew	1.18 (0.57,2.46)**	0.659**	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

** Group-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-20 for further analysis of this interaction.

Table 19-26. (Continued)
Analysis of Lupus Panel: MSK Parietal Antibody

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Present	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	171	3.5	0.88 (0.59,1.33)	0.533
Medium	172	2.9		
High	168	1.8		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)[a]			
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
511	0.88 (0.59,1.33)	0.533	

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-26. (Continued)
Analysis of Lupus Panel: MSK Parietal Antibody

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Present	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,051	2.4		
Background RH	367	1.4	0.60 (0.23,1.60)	0.312
Low RH	256	3.1	1.29 (0.57,2.91)	0.537
High RH	255	2.4	0.94 (0.38,2.33)	0.891
Low plus High RH	511	2.7	1.11 (0.57,2.17)	0.753

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	1,035			AGE (p=0.027) CSMOK (p=0.073) ALC (p=0.064)
Background RH	365	0.55 (0.21,1.45)	0.226	
Low RH	253	1.21 (0.54,2.74)	0.643	
High RH	251	1.01 (0.40,2.51)	0.989	
Low plus High RH	504	1.12 (0.57,2.18)	0.750	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-26. (Continued)
Analysis of Lupus Panel: MSK Parietal Antibody

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Present/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	0.7 (289)	3.7 (295)	2.0 (294)	1.17 (0.87,1.57)	0.319
5	0.3 (294)	4.1 (292)	2.1 (292)	1.16 (0.89,1.51)	0.279
6[c]	0.3 (293)	4.1 (292)	2.1 (292)	1.16 (0.87,1.55)	0.307

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	878	1.29 (0.94,1.77)	0.118	AGE (p=0.012) CSMOK (p=0.072)
5	878	1.25 (0.95,1.66)	0.114	AGE (p=0.013) CSMOK (p=0.075)
6[d]	877	1.29 (0.95,1.76)	0.104	AGE (p=0.011) CSMOK (p=0.069)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

The unadjusted and adjusted analysis in Models 4 through 6 did not reveal any significant associations between current dioxin and the existence of parietal cell antibodies (Table 19-26(g,h): $p>0.10$). The covariates age and current cigarette smoking were included in each of the final models for Models 4, 5, and 6.

Lupus Panel: Rheumatoid Factor

The unadjusted Model 1 analysis of rheumatoid factor disclosed no significant differences between Ranch Hands and Comparisons (Table 19-27(a): $p>0.11$ for all contrasts). In the adjusted analysis, the relative risk was marginally significant for officers (Table 19-27(b): $p=0.082$, Adj. RR=0.72), but was nonsignificant for all other occupational categories ($p>0.37$).

A significant negative association between initial dioxin and rheumatoid factor was revealed in the unadjusted Model 2 analysis (Table 19-27(c): $p=0.028$, Est. RR=0.80). The percentage of Ranch Hands with the lupus panel rheumatoid factor present were 18.1, 12.2, and 13.1 percent for the low, medium, and high initial dioxin categories. In the adjusted analysis, initial dioxin-by-age and initial dioxin-by-occupation interactions were significant (Table 19-27(d): $p=0.007$ and $p=0.037$). Stratified results are presented in Appendix Table O-2-21. After removing the interactions from the model, the adjusted relative risk was marginally significant ($p=0.058$, Adj. RR=0.80).

In the unadjusted Model 3 analysis, the difference in the percentage of participants with a positive rheumatoid factor between the high Ranch Hand category (10.6%) and the Comparison category (16.8%) was significant (Table 19-27(e): $p=0.012$, Est. RR=0.57). All other contrasts were nonsignificant ($p>0.21$). In the adjusted analysis, the categorized dioxin-by-occupation and categorized dioxin-by-physical activity index interactions were significant (Table 19-27(f): $p=0.004$ and $p=0.019$). Stratified results are presented in Appendix Table O-2-21. After removing the interactions from the model, the high Ranch Hand versus Comparison contrast remained significant ($p=0.035$, Adj. RR=0.62) and the other contrasts remained nonsignificant ($p>0.31$). Age and current alcohol use were covariates retained in the final adjusted model.

The inverse association between current dioxin and a positive rheumatoid factor was significant in the unadjusted and adjusted analyses of Models 4 and 5 (Table 19-27(g,h): $p=0.038$, Est. RR=0.87 and $p=0.023$, Est. RR=0.88 for the unadjusted analyses of Models 4 and 5; $p=0.013$, Adj. RR=0.83 and $p=0.008$, Adj. RR=0.85 for the adjusted analyses of Models 4 and 5). The adjusted analysis of Model 6 was marginally significant (Table 19-27(h): $p=0.053$, Adj. RR=0.88). However, when occupation was removed from Model 4, the association became marginally significant (Table O-13-17(c): $p=0.072$, Adj. RR=0.88). The association became nonsignificant (Appendix Table O-3-17: $p=0.207$) in Model 6 after removing occupation from the final model. Models 4, 5, and 6 each were adjusted for age, occupation, and the physical activity index.

Table 19-27.
Analysis of Lupus Panel: Rheumatoid Factor

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	Group	n	Percent Present	Est. Relative Risk (95% C.I.)	p-Value
All	***Ranch Hand***	***936***	***15.2***	***0.89 (0.71,1.13)***	***0.367***
	Comparison	***1,264***	***16.7***		
Officer	Ranch Hand	363	15.2	0.74 (0.51,1.06)	0.118
	Comparison	492	19.5		
Enlisted Flyer	Ranch Hand	160	13.8	0.78 (0.44,1.39)	0.484
	Comparison	200	17.0		
Enlisted Groundcrew	Ranch Hand	413	15.7	1.13 (0.80,1.61)	0.551
	Comparison	572	14.2		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks[a]
All	***0.90 (0.71,1.14)***	***0.371***	AGE (p=0.005) ALC (p=0.097)
Officer	0.72 (0.50,1.04)	0.082	
Enlisted Flyer	0.81 (0.45,1.45)	0.472	
Enlisted Groundcrew	1.16 (0.81,1.67)	0.405	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-27. (Continued)
Analysis of Lupus Panel: Rheumatoid Factor

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Present	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	171	18.1	0.80 (0.65,0.98)	0.028
Medium	172	12.2		
High	168	13.1		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)[c]			
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
511	0.80 (0.64,1.01)**	0.058**	INIT*OCC (p=0.007) INIT*AGE (p=0.037)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

** Log_2 (initial dioxin)-by-covariate interactions ($p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of these interactions; refer to Appendix Table O-2-21 for further analysis of these interactions.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-27. (Continued)
Analysis of Lupus Panel: Rheumatoid Factor

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Present	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,051	16.8		
Background RH	367	16.1	0.96 (0.70,1.33)	0.823
Low RH	256	18.4	1.11 (0.78,1.58)	0.575
High RH	255	10.6	0.57 (0.37,0.88)	0.012
Low plus High RH	511	14.5	0.83 (0.62,1.11)	0.211

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	1,035			DXCAT*OCC (p=0.004) DXCAT*PHYACT (p=0.019) AGE (p=0.084) ALC (p=0.093)
Background RH	365	0.95 (0.68,1.32)**	0.744**	
Low RH	253	1.08 (0.75,1.55)**	0.670**	
High RH	251	0.62 (0.40,0.97)**	0.035**	
Low plus High RH	504	0.86 (0.63,1.16)**	0.312**	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

** Categorized dioxin-by-covariate interactions ($p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of these interactions; refer to Appendix Table O-2-21 for further analysis of these interactions.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-27. (Continued)
Analysis of Lupus Panel: Rheumatoid Factor

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Present/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	16.6 (289)	17.6 (295)	11.2 (294)	0.87 (0.76,0.99)	0.038
5	18.0 (294)	17.1 (292)	10.3 (292)	0.88 (0.79,0.98)	0.023
6[c]	18.1 (293)	17.1 (292)	10.3 (292)	0.91 (0.81,1.03)	0.126

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	878	0.83 (0.72,0.96)	0.013	AGE (p=0.094) OCC (p=0.070) PHYACT (p=0.070)
5	878	0.85 (0.75,0.96)	0.008	AGE (p=0.084) OCC (p=0.068) PHYACT (p=0.071)
6[d]	877	0.88 (0.77,1.00)	0.053	AGE (p=0.056) OCC (p=0.074) PHYACT (p=0.067)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Lupus Panel: B Cell Clones Detected by Serum Protein Electrophoresis

In the unadjusted and adjusted Model 1 analyses of B cell clones detected by serum protein electrophoresis, no significant differences between Ranch Hands and Comparisons were found (Table 19-28(a,b): $p \geq 0.12$ for all contrasts). Age was the only significant covariate in the adjusted model.

The association between initial dioxin and B cell clones detected by serum protein electrophoresis was nonsignificant in the unadjusted and adjusted Model 2 analyses (Table 19-28(c,d): $p=0.838$ and $p=0.325$). Age and the physical activity index were included in the final adjusted model.

In the unadjusted Model 3 analyses of B cell clones detected by serum protein electrophoresis, the contrast between the background Ranch Hand and the Comparison categories was marginally significant (Table 19-28(e): $p=0.072$, Est. RR=1.97). The remaining unadjusted contrasts and all of the adjusted contrasts were nonsignificant (Table 19-28(e,f): $p>0.13$). In the final adjusted model, age and occupation were retained.

The association between current dioxin and B cell clones detected by serum protein electrophoresis was nonsignificant in the unadjusted and adjusted analyses of Models 4, 5, and 6 (Table 19-28(g,h): $p>0.14$ for all analyses). The current dioxin-by-current alcohol use interaction was significant in Models 5 and 6 (Table 19-28(h): $p=0.030$ and $p=0.037$). Stratified results for these interactions are presented in Appendix Table O-2-22. Age also was significant in all three adjusted models.

Lupus Panel: Other Antibodies (ANA and MSK)

Unadjusted and adjusted results from the Model 1, 2, and 3 analyses of other antibodies (ANA and MSK) were nonsignificant (Table 19-29(a-f): $p \geq 0.15$ for all analyses). Race was included in each of the adjusted models. The physical activity index also was retained in Models 1 and 3.

In Models 4, 5, and 6, the unadjusted analyses of other antibodies (ANA and MSK) showed no significant association with current dioxin (Table 19-29(g): $p>0.42$ for all models). The adjusted analyses of Models 4 and 5 retained no significant covariates; therefore, the results are identical to the unadjusted results. In the adjusted analysis of Model 6, the current dioxin-by-race interaction was significant (Table 19-29(h): $p=0.046$). Results for each race stratum are presented in Appendix Table O-2-23. After removing the current dioxin-by-race interaction from the final model, the association between current dioxin and other antibodies (ANA and MSK) was nonsignificant ($p=0.417$).

Table 19-28.
Analysis of Lupus Panel: B Cell Clones Detected by Serum Protein Electrophoresis

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Percent Present**	**Est. Relative Risk (95% C.I.)**	**p-Value**
All	*Ranch Hand*	*936*	*2.4*	*1.36 (0.75,2.47)*	*0.392*
	Comparison	*1,264*	*1.7*		
Officer	Ranch Hand	363	3.3	2.07 (0.84,5.11)	0.168
	Comparison	492	1.6		
Enlisted Flyer	Ranch Hand	160	3.8	1.26 (0.40,3.98)	0.922
	Comparison	200	3.0		
Enlisted Groundcrew	Ranch Hand	413	1.0	0.69 (0.21,2.31)	0.754
	Comparison	572	1.4		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	**Adj. Relative Risk (95% C.I.)**	**p-Value**	**Covariate Remarks[a]**
All	*1.35 (0.74,2.45)*	*0.328*	AGE (p=0.010)
Officer	2.05 (0.83,5.08)	0.120	
Enlisted Flyer	1.25 (0.39,3.95)	0.706	
Enlisted Groundcrew	0.69 90.21,2.30)	0.546	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-28. (Continued)
Analysis of Lupus Panel: B Cell Clones Detected by Serum Protein Electrophoresis

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Present	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	171	1.2	1.05 (0.66,1.68)	0.838
Medium	172	2.9		
High	168	1.8		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)[c]			
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
511	1.30 (0.78,2.17)	0.325	AGE ($p<0.001$) PHYACT ($p=0.102$)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-28. (Continued)
Analysis of Lupus Panel: B Cell Clones Detected by Serum Protein Electrophoresis

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Present	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,051	1.9		
Background RH	367	3.3	1.97 (0.94,4.12)	0.072
Low RH	256	1.6	0.77 (0.26,2.29)	0.640
High RH	255	2.4	1.13 (0.45,2.88)	0.789
Low plus High RH	511	2.0	0.95 (0.44,2.07)	0.906

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	1,051			AGE (p=0.045) OCC (p=0.071)
Background RH	367	1.79 (0.84,3.83)	0.134	
Low RH	256	0.70 (0.23,2.07)	0.514	
High RH	255	1.36 (0.51,3.64)	0.534	
Low plus High RH	511	0.97 (0.44,2.13)	0.943	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-28. (Continued)
Analysis of Lupus Panel: B Cell Clones Detected by Serum Protein Electrophoresis

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Present/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	2.4 (289)	3.1 (295)	2.0 (294)	0.85 (0.63,1.16)	0.297
5	2.7 (294)	3.1 (292)	1.7 (292)	0.88 (0.69,1.12)	0.306
6[c]	2.7 (293)	3.1 (292)	1.7 (292)	0.82 (0.63,1.07)	0.147

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	878	0.91 (0.66,1.27)	0.572	AGE (p=0.006)
5	869	0.92 (0.71,1.20)**	0.543**	CURR*ALC (p=0.030) AGE (p=0.005)
6[d]	868	0.87 (0.65,1.16)**	0.340**	CURR*ALC (p=0.037) AGE (p=0.006)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

** Log_2 (current dioxin + 1)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this Interaction; refer to Appendix Table O-2-22 for further analysis of this interaction.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 19-29.
Analysis of Lupus Panel: Other Antibodies (ANA and MSK)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	Group	n	Percent Present	Est. Relative Risk (95% C.I.)	p-Value
All	***Ranch Hand***	***932***	***3.1***	***0.76 (0.48,1.21)***	***0.300***
	Comparison	***1,261***	***4.0***		
Officer	Ranch Hand	362	3.0	0.64 (0.31,1.32)	0.297
	Comparison	490	4.7		
Enlisted Flyer	Ranch Hand	159	4.4	0.88 (0.33,2.35)	0.988
	Comparison	200	5.0		
Enlisted Groundcrew	Ranch Hand	411	2.7	0.85 (0.40,1.81)	0.808
	Comparison	571	3.2		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks[a]
All	***0.76 (0.48,1.21)***	***0.246***	RACE (p=0.032) PHYACT (p=0.042)
Officer	0.64 (0.31,1.33)	0.228	
Enlisted Flyer	0.89 (0.33,2.40)	0.814	
Enlisted Groundcrew	0.84 (0.39,1.80)	0.653	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-29. (Continued)
Analysis of Lupus Panel: Other Antibodies (ANA and MSK)

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Present	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	170	1.2	1.15 (0.77,1.71)	0.508
Medium	172	4.7		
High	167	3.0		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)[c]			
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
509	1.12 (0.76,1.67)	0.569	RACE (p=0.137)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-29. (Continued)
Analysis of Lupus Panel: Other Antibodies (ANA and MSK)

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Present	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,048	4.3		
Background RH	365	3.3	0.77 (0.40,1.49)	0.444
Low RH	255	2.4	0.53 (0.22,1.26)	0.150
High RH	254	3.5	0.81 (0.39,1.68)	0.566
Low plus High RH	509	2.9	0.67 (0.37,1.21)	0.184

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	1,046			RACE (p=0.080) PHYACT (p=0.051)
Background RH	365	0.77 (0.40,1.49)	0.438	
Low RH	255	0.54 (0.23,1.29)	0.168	
High RH	254	0.78 (0.38,1.63)	0.510	
Low plus High RH	509	0.66 (0.37,1.21)	0.180	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-29. (Continued)
Analysis of Lupus Panel: Other Antibodies (ANA and MSK)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Present/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	3.1 (287)	2.7 (294)	3.4 (293)	1.07 (0.83,1.39)	0.595
5	3.4 (292)	2.7 (291)	3.1 (291)	1.05 (0.83,1.31)	0.697
6[c]	3.4 (291)	2.8 (291)	3.1 (291)	1.10 (0.87,1.41)	0.424

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	874	1.07 (0.83,1.39)	0.595	
5	874	1.05 (0.83,1.31)	0.697	
6[d]	873	1.11 (0.87,1.41)**	0.417**	CURR*RACE (p=0.046)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

** Log_2 (current dioxin + 1)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-23 for further analysis of this interaction.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Lupus Panel: Summary Index

The unadjusted and adjusted Model 1 analyses of the lupus panel summary index showed no significant differences between Ranch Hands and Comparisons (Table 19-30(a,b): $p>0.12$ for all contrasts). Age and race were significant covariates in the adjusted analysis.

A marginally significant negative association between the lupus panel summary index and initial dioxin was discovered in the unadjusted analysis of Model 2 (Table 19-30(c): $p=0.067$, Est. RR=0.88). However, the association became nonsignificant after adjusting for age and current alcohol use (Table 19-30(d): $p=0.658$).

In the unadjusted Model 3 analysis of the lupus panel summary index, the contrasts between the high Ranch Hand category and Comparisons and between the low plus high Ranch Hand category and Comparisons were significant (Table 19-30(e): $p=0.002$, Est. RR=0.62 for high Ranch Hands vs. Comparisons; $p=0.021$, Est. RR=0.77 for low plus high Ranch Hands vs. Comparisons). The percentage of participants with abnormal lupus panel index results were 41.4 percent for Comparisons, 31.1 percent in the high Ranch Hand category, and 35.8 percent in the low plus high Ranch Hand category. The contrasts of the background Ranch Hand and low Ranch Hand categories versus Comparisons were nonsignificant ($p>0.68$). In the adjusted analysis, the high Ranch Hand versus Comparison and the low plus high Ranch Hand versus Comparison contrasts remained significant (Table 19-30(f): $p=0.019$, Adj. RR=0.70 for high Ranch Hands vs. Comparisons; $p=0.040$, Adj. RR=0.79 for low plus high Ranch Hands vs. Comparisons). The background Ranch Hand and low Ranch Hand contrasts remained nonsignificant ($p>0.39$). Age, race, and current cigarette smoking were included in the final adjusted model.

A significant negative association between current dioxin and the lupus panel summary index was detected in the unadjusted analyses of Models 4, 5, and 6 (Table 19-30(g): $p=0.028$, Est. RR=0.90 for Model 4; $p=0.042$, Est. RR=0.92 for Model 5; $p=0.030$, Est. RR=0.91 for Model 6). However, after adjusting each model for age and lifetime cigarette smoking history, the associations became nonsignificant (Table 19-30(h): $p=0.248$ for Model 4; $p=0.259$ for Model 5; and $p=0.294$ for Model 6).

Longitudinal Analysis

Longitudinal analyses for the CD4-CD8 ratio examined the paired difference between the measurements from 1985 and 1992. These paired differences measured the change in the ratio over time. Each of the three models used in the longitudinal analysis were adjusted for age and the CD4-CD8 ratio measured in 1985. The analyses of Models 2 and 3 also were adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

CD4-CD8 Ratio

Results from the Model 1 and Model 2 longitudinal analyses of the ratio of CD4 to CD8 were nonsignificant (Table 19-31(a,b): $p>0.10$ for all analyses).

Table 19-30.
Analysis of Lupus Panel: Summary Index

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	Group	n	Percent Abnormal	Est. Relative Risk (95% C.I.)	p-Value
All	***Ranch Hand***	***933***	***37.1***	***0.88 (0.74,1.05)***	***0.170***
	Comparison	***1,263***	***40.1***		
Officer	Ranch Hand	363	41.0	0.90 (0.68,1.18)	0.481
	Comparison	492	43.7		
Enlisted Flyer	Ranch Hand	159	38.4	0.97 (0.64,1.49)	0.989
	Comparison	200	39.0		
Enlisted Groundcrew	Ranch Hand	411	33.1	0.83 (0.64,1.09)	0.196
	Comparison	571	37.3		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks[a]
All	***0.87 (0.73,1.04)***	***0.124***	AGE ($p<0.001$) RACE ($p=0.042$)
Officer	0.88 (0.67,1.16)	0.368	
Enlisted Flyer	0.97 (0.63,1.49)	0.875	
Enlisted Groundcrew	0.83 (0.63,1.09)	0.179	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-30. (Continued)
Analysis of Lupus Panel: Summary Index

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Abnormal	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	170	40.6	0.88 (0.76,1.01)	0.067
Medium	172	33.7		
High	167	32.9		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)[c]			
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
502	0.97 (0.83,1.13)	0.658	AGE (p<0.001) ALC (p=0.123)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-30. (Continued)
Analysis of Lupus Panel: Summary Index

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,050	41.4		
Background RH	366	39.6	0.96 (0.75,1.22)	0.720
Low RH	255	40.4	0.94 (0.71,1.25)	0.685
High RH	254	31.1	0.62 (0.46,0.84)	0.002
Low plus High RH	509	35.8	0.77 (0.62,0.96)	0.021

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	1,048			AGE ($p<0.001$) RACE ($p=0.081$) CSMOK ($p=0.101$)
Background RH	366	0.90 (0.70,1.15)	0.397	
Low RH	255	0.89 (0.67,1.18)	0.408	
High RH	254	0.70 (0.52,0.94)	0.019	
Low plus High RH	509	0.79 (0.63,0.99)	0.040	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-30. (Continued)
Analysis of Lupus Panel: Summary Index

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Abnormal/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	39.9 (288)	41.5 (294)	30.7 (293)	0.90 (0.82,0.99)	0.028
5	39.6 (293)	42.6 (291)	29.9 (291)	0.92 (0.85,1.00)	0.042
6[c]	39.7 (292)	42.6 (291)	29.9 (291)	0.91 (0.83,0.99)	0.030

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	874	0.94 (0.85,1.04)	0.248	AGE (p<0.001) PACKYR (p=0.068)
5	874	0.95 (0.88,1.04)	0.259	AGE (p<0.001) PACKYR (p=0.067)
6[d]	873	0.95 (0.87,1.04)	0.294	AGE (p<0.001) PACKYR (p=0.061)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for $\log_2$ total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for $\log_2$ total lipids.

[d] Adjusted for $\log_2$ total lipids in addition to covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 19-31.
Longitudinal Analysis of CD4-CD8 Ratio

a) MODEL 1: RANCH HANDS VS. COMPARISONS							
		Mean[a]/(n) Examination					
Occupational Category	Group	1985	1987	1992	Exam. Mean Change[b]	Difference of Exam. Mean Change	p-Value[c]
All	*Ranch Hand*	*1.635 (303)*	*1.951 (284)*	*1.552 (303)*	*-0.083*	*0.029*	*0.109*
	Comparison	*1.600 (401)*	*1.903 (386)*	*1.488 (401)*	*-0.112*		
Officer	Ranch Hand	1.640 (126)	1.910 (120)	1.553 (126)	-0.087	0.007	0.534
	Comparison	1.591 (144)	1.934 (137)	1.498 (144)	-0.093		
Enlisted Flyer	Ranch Hand	1.570 (58)	1.959 (55)	1.493 (58)	-0.078	0.007	0.536
	Comparison	1.497 (69)	1.845 (67)	1.413 (69)	-0.084		
Enlisted Groundcrew	Ranch Hand	1.662 (119)	1.992 (109)	1.579 (119)	-0.082	0.056	0.227
	Comparison	1.647 (188)	1.902 (182)	1.509 (188)	-0.138		

[a] Transformed from natural logarithm scale.

[b] Difference between 1992 and 1985 examination means after transformation to original scale.

[c] P-value is based on analysis of natural logarithm of CD4-CD8 ratio; results adjusted for natural logarithm of CD4-CD8 ratio in 1985 and age in 1992.

Note: Summary statistics for 1987 are provided for reference purposes for participants who attended the 1985, 1987, and 1992 examinations.

Table 19-31. (Continued)
Longitudinal Analysis of CD4-CD8 Ratio

b) MODEL 2: RANCH HANDS — INITIAL DIOXIN					
Initial Dioxin Category Summary Statistics				Analysis Results for Log_2 (Initial Dioxin)[b]	
	Mean[a]/(n) Examination				
Initial Dioxin	1985	1987	1992	Adj. Slope (Std. Error)	p-Value
Low	1.675 (52)	1.942 (50)	1.535 (52)	-0.0086 (0.0165)	0.602
Medium	1.654 (58)	2.139 (56)	1.656 (58)		
High	1.627 (64)	1.935 (56)	1.577 (64)		

[a] Transformed from natural logarithm scale.

[b] Results based on difference between natural logarithm of CD4-CD8 ratio in 1985 and natural logarithm of CD4-CD8 ratio in 1992 versus $\log_2$ (initial dioxin); results adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of blood draw for dioxin, natural logarithm of 1985 CD4-CD8 ratio, and age in 1992.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.
Summary statistics for 1987 are provided for reference purposes for participants who attended the 1985, 1987, and 1992 examinations.

Table 19-31. (Continued)
Longitudinal Analysis of CD4-CD8 Ratio

c) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY						
	Mean[a]/(n) Examination					
Dioxin Category	1985	1987	1992	Exam. Mean Change[b]	Difference of Exam. Mean Change	p-Value[c]
Comparison	1.590 (359)	1.896 (350)	1.478 (359)	-0.112		
Background RH	1.609 (117)	1.863 (112)	1.483 (117)	-0.126	-0.014	0.624
Low RH	1.643 (78)	1.991 (76)	1.565 (78)	-0.078	0.034	0.087
High RH	1.656 (96)	2.018 (86)	1.610 (96)	-0.047	0.066	0.303
Low plus High RH	1.650 (174)	2.005 (162)	1.590 (174)	-0.061	0.051	0.078

[a] Transformed from natural logarithm scale.

[b] Difference between 1992 and 1985 examination means after transformation to original scale.

[c] P-value is based on analysis of natural logarithm of CD4-CD8 ratio; results adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, natural logarithm of CD4-CD8 ratio in 1985, and age in 1992.

Note: RH = Ranch Hand.
Comparison: Current Dioxin $\leq$10 ppt.
Background (Ranch Hand): Current Dioxin $\leq$10 ppt.
Low (Ranch Hand): Current Dioxin >10 ppt, 10 ppt < Initial Dioxin $\leq$143 ppt.
High (Ranch Hand): Current Dioxin >10 ppt, Initial Dioxin >143 ppt.
Summary statistics for 1987 are provided for reference purposes for participants who attended the 1985, 1987, and 1992 examinations.

The Model 3 longitudinal analysis exploring differences of examination mean change between 1985 and 1992 for the CD4-CD8 ratio disclosed marginally significant differences for low Ranch Hands versus Comparisons and low plus high Ranch Hands versus Comparisons (Table 19-31(c): $p=0.087$, Diff. of Exam. Mean Change=0.034 and $p=0.078$ Diff. of Exam. Mean Change=0.051 respectively). These results indicated that the decrease in the CD4-CD8 ratio between 1985 and 1992 was greater for Comparisons than for Ranch Hands. Between 1985 and 1992, differences in CD4-CD8 ratio for background and high Ranch Hands did not differ significantly from Comparisons.

DISCUSSION

Immunologic competence was assessed by analyzing data from skin tests for delayed hypersensitivity response, cell surface marker studies on a randomized subset of the study population, immunoglobulin quantitation, and autoantibody detection. The absence of a response to a series of skin test antigens is usually indicative of an impaired immune defense mechanism (anergy). Anergy can occur in elderly individuals in the setting of certain viral, bacterial, and fungal infections or with advanced protein deficiency, underlying malignancy, or treatment with corticosteroids, other immunosuppressive agents, or chemotherapy. Skin tests for delayed cutaneous hypersensitivity (DCH) are occasionally used to test for anergy as a prognostic indicator in individuals in compromised states such as those with AIDS or those at risk of infection following surgery.

Evaluation of the human immune system is divided into separate segments for humoral and cellular immunity. Circulating in the plasma phase of blood, the humoral segment consists of the immunoglobulin and complement proteins, some of which are also prominent at exposed sites of the body such as mucosal surfaces. The serum immunoglobulins are secreted by plasma cells in the bone marrow and are regulated in a sequence of events modulated by macrophages and memory lymphocytes. The immunoglobulins serve as a defense against bacterial infections and the blood-borne phase of viral infections.

Quantitative analysis of IgA, IgG, and IgM, give an overall view of B-cell integrity when related to the expected reference range of values. Selective deficiency of one or more of these antibody classes, whether congenital or acquired, may be associated with increased susceptibility to infections. Elevations of these immunoglobulins in a polyclonal pattern are frequently an indication of chronic infections (perhaps due to impairment of another segment of the immune response), of chronic inflammation such as in autoimmune disease, or of faulty regulation of B-cell responses such as occurs in cirrhosis. Selective elevation of a monoclonal segment of any immunoglobulin (detected by visual examination of serum protein electrophoresis as B cell clones) is a strong indicator of faulty regulation or actual autonomy of plasma cells or lymphocytes and may be an early hallmark of numerous conditions including plasmacytoma, multiple myeloma, chronic lymphocytic leukemia and lymphoma, and smoldering myeloma. Occasionally there may be a cluster of more than one small spike of immunoglobulin in the presence of other normal immunoglobulins. Invariably, this type of oligoclonal banding is associated with some alteration of the immune system (e.g., primary bone marrow involvement, inappropriate regulation, or immunosuppression as in organ transplant recipients). Thus, both quantitative and qualitative parameters of the serum immunoglobulins can give information on the integrity of B-cell responses.

Further evidence for the integrity of the immune system in aging individuals is the presence or absence of various autoantibodies. These autoantibodies measured in the lupus panel are considered to be abnormalities when present. While they can be specific and sensitive markers for autoimmune diseases (especially at high titers), they also occur as almost renegade substances when the immune system ages and as such are markers for deterioration of the B-cell regulatory process of immunity.

Cellular immunity consists of both granulocytic and lymphocytic processes. Abnormalities of granulocytes can frequently be discerned from examination of the peripheral blood smear as part of the complete blood count. In addition, the infectious history of individuals is usually sufficient to ascertain whether granulocytic deficiency is a consideration. Chapter 16, Hematologic Assessment, discusses the effect of dioxin on the components of these cells.

The lymphocytic segment of the immune response can be broadly evaluated by skin testing against multiple fungal, bacterial, or viral agents. The response to skin tests is dependent in part on the infection exposure history of the patient, and so is probably better used in the diagnosis of specific diseases than in an overall examination of lymphocyte function, although it does have the particular merit of demonstrating the presence or absence of the response in vivo, where it must be effective for the patient to remain healthy.

The total number of circulating lymphocytes provides information relative to the basic cellular quantity of cells present and available in the body for mounting an immune response. Examination of the surface marker proteins on the surfaces of these lymphocytes by flow cytometry is an excellent means of evaluating whether the regulatory interactions between T cells, B cells, and monocytes are intact. An alteration in the percentages of any of these categories can be considered presumptive evidence of an inability to recognize and destroy foreign infectious agents or tumor cells. The marker for total T cells was CD3, which is further broken down into the subpopulations of CD4 (helper cells) and CD8 (suppressor cells); CD4 and CD8 should be mutually exclusive. The ratio of CD4 to CD8 describes whether the regulation is in balance. Expected values for the CD4 to CD8 ratio are roughly 0.9 to 3.5. Ratios substantially below 1.0 are to be expected in patients immunosuppressed with cyclosporine and also those with active human immunodeficiency virus infection that involves primarily the CD4 positive cells. Activation of T cells results in the new synthesis of IL-2 receptor molecules on the surface of lymphocytes. This IL-2 receptor also is designated CD25, and its presence in excess is an indicator of recent stimulus to the immune system by virtually any type of antigen—for example, infectious organisms or transplanted organs. The surface marker for B cell CD20 gives an indication of the balance between cellular immunity and the ability to mount a B-cell response with production of specific antibodies. The CD14 marker is specific for monocytes that are essential for the correct transfer of stimulatory information from the (foreign) antigen processing segment to the antibody turn-on segment of a B-cell response. The CD5 marker frequently is found on abnormal subsets of B cells that predominate in chronic lymphocytic leukemia or that are responsible for autoimmune disease. The CD16 and CD56 markers are found on natural killer (NK) lymphocytes that provide a strong line of defense against the growth of neoplasms. Various combinations of these markers also were studied to detect double labeled cells that could indicate abnormalities such as very immature lymphocytes (e.g., CD4

with CD8, which should be mutually exclusive subsets). Additional double labeled studies were configured to provide better resolution of normal subsets (e.g., CD3 with CD25 to focus on true T cells that are activated).

Interpretation of alterations in the relative amounts of B cells, T cells and their subsets, and monocytes is based on the expectation that all aspects of the immune system must be intact to prevent infections and to guard against development of tumors with unusual surface antigens. The antibodies specific for tumors can either help to destroy them by binding complement and lysing the cells or stabilize them if those antibodies attach to the tumor surface without binding complement, thereby blocking immune recognition and destruction of tumor cells. The T cells also have antigen receptors on their surfaces that similarly call into play the destructive power of the entire lymphocyte cell line in an antitumor attack. T cells stimulated by IL-2 have even greater capacity to attack and destroy foreign cells. NK cells have still greater destructive capacity, but they act on a nonspecific basis and are probably simply recruited into regions of foreign antigens and tumors by the other recognition factors.

The immunologic evaluation performed on study participants went far beyond typical medical examinations employed for general health assessments. This evaluation included elements of measurement frequently used individually to define specific diseases. As a test panel battery, this assessment provided an in-depth, broad review of immunologic parameters designed to detect abnormalities or variances that may or may not carry clinical import.

This thorough evaluation of the immune system did not reveal any relationships between dioxin exposure and physiologic abnormalities that could be considered clinically significant. Some individual elements showed statistical significance, although the magnitude of such relationships was small and certainly not to be interpreted as conveying health risk. An inverse relationship was found with dioxin exposure and the presence of autoantibodies to MSK smooth muscle, rheumatoid factor, and the lupus panel summary index. Although a negative test is usually considered to be normal, it is likely that a certain percentage of individuals would test as positive. The statistically significant negative association may indicate a highly sensitive but clinically insignificant first indication of a generalized immune suppression. Clarification of the relevance of these findings to a hypothesis of dioxin-induced immune suppression will require analysis of data from future physical examinations.

Conversely, because a normally active immune system does show development of some autoantibodies with age, finding fewer than expected autoantibodies may reflect some diminished capacity of the immune system to respond to stimuli. This interpretation is not typically evoked in otherwise healthy individuals; however, in this population study, fewer than expected autoantibodies may be a highly sensitive indication of immune suppression secondary to dioxin exposure. This issue cannot be resolved in the current cycle of study but should be evaluated in future examinations to determine clinical significance, if any.

Other findings correlating with dioxin exposure, including low IgG, presence of thyroid microsomal antibody, and alterations in lymphocyte surface markers, were also difficult to attribute to specific clinical deficiencies, because they were mild variations. A mild relationship between serum IgA concentrations and dioxin continued from the previous study in 1987. Although the magnitude of this effect was small, its statistical significance coupled

with continuity over time suggests a possible relationship that should be further evaluated because elevated IgA may indicate liver disease, chronic inflammation, or selective immune dysfunction (albeit mild).

In many instances, statistical correlations exist between immunologic parameters and the covariates age, tobacco use, alcohol consumption, and exercise. Consequently, it is important to account for this potential source of variation between Ranch Hands and Comparisons. Recent work has demonstrated the particular effect of tobacco use on the immune response (53-57).

In summary, these findings do not provide evidence of a clinically significant dose-response effect for body burden of dioxin on parameters of immunologic assessment. The minor statistically significant relationships that do have a small magnitude bear long-term evaluation for trend development, but at present they cannot be interpreted to indicate specific health impairment due to immune system dysfunction.

SUMMARY

The immunology assessment was based on physical examination data and laboratory data. Each of the variables was analyzed for associations with group (Model 1), initial lipid-adjusted dioxin (Model 2), categorized initial dioxin (Model 3), current lipid-adjusted dioxin (Model 4), and current whole-weight dioxin (Models 5 and 6). Tables 19-32 through 19-35 summarize the results. A summary of group-by-covariate and dioxin-by-covariate interactions is provided in Table 19-36.

Model 1: Group Analyses

In the unadjusted analyses of Model 1, the immunoglobulin IgG and the lupus panel ANA test showed marginally significant inverse relationships with group. The lupus panel thyroid microsomal antibody showed a significant positive association with group. The officer Ranch Hands had significantly or marginally significantly higher mean CD3 cell, CD4 cell, and CD5 cell counts than the officer Comparisons. The enlisted flyer Ranch Hands had marginally significantly lower mean CD8 cell and CD16+56 cell counts than the enlisted flyer Comparisons. CD5 with CD20 double labelled cells for measurements above zero showed enlisted groundcrew Ranch Hands to have significantly higher mean CD5 with CD20 values than the enlisted groundcrew Comparisons. The enlisted groundcrew Ranch Hands had a marginally significantly lower percentage of positive ANA test results than the enlisted groundcrew Comparisons.

Adjusting for covariates in Model 1 revealed a marginally significant positive association between group and CD20 cells and significant inverse associations between group and the immunoglobulin IgG and group and the lupus panel ANA test. Officer Ranch Hands had a marginally higher percentage of abnormal findings for the composite skin test diagnosis and the lupus panel MSK parietal antibody than the officer Comparisons. The officer Ranch Hands had a significantly lower percentage of positive rheumatoid factor findings than the officer Comparisons. The enlisted flyer Ranch Hands had significantly or marginally significantly lower mean CD8 cell, CD14 cell, CD25 cell, and CD3 with CD25 cell values

Table 19-32.
Summary of Group Analyses (Model 1) for Immunology Variables
(Ranch Hands vs. Comparisons)

	UNADJUSTED			
Variable	All	Officer	Enlisted Flyer	Enlisted Groundcrew
Physical Examination				
Composite Skin Test Diagnosis (D)	NS	NS	NS	NS
Laboratory: Cell Surface Marker				
CD3 Cells (C)	NS	+0.039	ns	NS
CD4 Cells (C)	NS	NS*	ns	NS
CD5 Cells (C)	NS	+0.035	NS	NS
CD8 Cells (C)	ns	NS	ns*	NS
CD14 Cells (C)	ns	NS	ns	ns
CD16+56 Cells (C)	ns	NS	ns*	ns
CD20 Cells (C)	NS	NS	ns	NS
CD25 Cells (C)	NS	NS	ns	NS
CD4-CD8 Ratio (C)	NS	NS	NS	NS
Double Labelled Cells: CD3 with CD25 (C)	NS	NS	ns	NS
Double Labelled Cells: CD5 with CD20 (D: Zero vs. Nonzero)	NS	NS	ns	NS
Double Labelled Cells: CD5 with CD20 (C: Nonzero Measurements)	NS	NS	ns	+0.046
Double Labelled Cells: CD4 with CD8 (D: Zero vs. Nonzero)	NS	NS	NS	ns
Double Labelled Cells: CD4 with CD8 (C: Nonzero Measurements)	ns	ns	NS	NS
Double Labelled Cells: CD3 with CD16+56 (D: Zero vs. Nonzero)	NS	ns	NS	NS
Double Labelled Cells: CD3 with CD16+56 (C: Nonzero Measurements)	NS	NS	NS	ns
Laboratory: TLC				
TLC (C)	NS	NS	ns	NS
Laboratory: Immunoglobulins				
IgA (C)	ns	ns	ns	NS
IgG (C)	ns*	ns	ns	ns
IgM (C)	ns	NS	ns	ns

Table 19-32. (Continued)
Summary of Group Analyses (Model 1) for Immunology Variables
(Ranch Hands vs. Comparisons)

	UNADJUSTED			
Variable	**All**	**Officer**	**Enlisted Flyer**	**Enlisted Groundcrew**
Laboratory:				
Lupus Panel				
ANA Test (D)	ns*	ns	ns	ns*
Thyroid Microsomal Antibody (D)	NS*	NS	NS	NS
MSK Smooth Muscle Antibody (D)	ns	NS	ns	ns
MSK Mitochondrial Antibody (D)	ns	NS	--	ns
MSK Parietal Antibody (D)	ns	NS	ns	ns
Rheumatoid Factor (D)	ns	ns	ns	NS
B Cell Clones Detected by Serum Protein Electrophoresis (D)	NS	NS	NS	ns
Other Antibodies (ANA and MSK) (D)	ns	ns	ns	ns
Summary Index (D)	ns	ns	ns	ns

C: Continuous analysis.
D: Discrete analysis.
+: Difference of means nonnegative for continuous analysis.
--: Analysis not presented due to sparse number of abnormalities.
NS or ns: Not significant ($p > 0.10$).
NS* or ns*: Marginally significant ($0.05 < p \leq 0.10$).
Note: P-value given if $p \leq 0.05$.
A capital "NS" denotes a relative risk 1.00 or greater for discrete analysis or difference of means nonnegative for continuous analysis; a lower case "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis.

Table 19-32. (Continued)
Summary of Group Analyses (Model 1) for Immunology Variables
(Ranch Hands vs. Comparisons)

	ADJUSTED			
Variable	**All**	**Officer**	**Enlisted Flyer**	**Enlisted Groundcrew**
Physical Examination				
Composite Skin Test Diagnosis (D)	NS	NS*	NS	NS
Laboratory: Cell Surface Marker				
CD3 Cells (C)	NS	NS	ns	NS
CD4 Cells (C)	NS	NS	ns	NS
CD5 Cells (C)	NS	NS	ns	NS
CD8 Cells (C)	ns	NS	ns*	NS
CD14 Cells (C)	**(ns)	NS	-0.021	NS
CD16+56 Cells (C)	ns	NS	ns	ns
CD20 Cells (C)	**(NS*)	**(NS)	**(ns)	**(NS)
CD25 Cells (C)	**(NS)	NS	-0.015	NS
CD4-CD8 Ratio (C)	**(NS)	**(NS)	**(NS)	**(NS)
Double Labelled Cells: CD3 with CD25 (C)	**(NS)	NS	-0.022	NS
Double Labelled Cells: CD5 with CD20 (D: Zero vs. Nonzero)	NS	NS	ns	NS
Double Labelled Cells: CD5 with CD20 (C: Nonzero Measurements)	NS	NS	ns	NS
Double Labelled Cells: CD4 with CD8 (D: Zero vs. Nonzero)	NS	NS	NS	ns
Double Labelled Cells: CD4 with CD8 (C: Nonzero Measurements)	ns	ns	NS	NS
Double Labelled Cells: CD3 with CD16+56 (D: Zero vs. Nonzero)	NS	ns	NS	NS
Double Labelled Cells: CD3 with CD16+56 (C: Nonzero Measurements)	ns	NS	ns	ns
Laboratory: TLC				
TLC (C)	NS	NS	ns	NS
Laboratory: Immunoglobulins				
IgA (C)	ns	ns	NS	NS
IgG (C)	ns*	ns	ns	ns
IgM (C)	**(ns)	**(NS)	**(ns)	**(ns)

Table 19-32. (Continued)
Summary of Group Analyses (Model 1) for Immunology Variables
(Ranch Hands vs. Comparisons)

	ADJUSTED			
Variable	All	Officer	Enlisted Flyer	Enlisted Groundcrew
Laboratory:				
Lupus Panel				
ANA Test (D)	ns*	ns	ns	ns*
Thyroid Microsomal Antibody (D)	****	****	****	****
MSK Smooth Muscle Antibody (D)	ns	NS	ns	ns
MSK Mitochondrial Antibody (D)	--	--	--	--
MSK Parietal Antibody (D)	**(ns)	**(NS*)	**(NS)	**(NS)
Rheumatoid Factor (D)	ns	ns*	ns	NS
B Cell Clones Detected by Serum Protein Electrophoresis (D)	NS	NS	NS	ns
Other Antibodies (ANA and MSK) (D)	ns	ns	ns	ns
Summary Index (D)	ns	ns	ns	ns

C: Continuous analysis.
D: Discrete analysis.
-: Difference of means negative for continuous analysis.
--: Analysis not performed due to sparse number of abnormalities.
NS or ns: Not significant (p>0.10).
NS* or ns*: Marginally significant (0.05<p≤0.10).
**(NS) or **(ns): Group-by-covariate interaction (p≤0.05); not significant when interaction is deleted; refer to Appendix O-2 for further analysis of this interaction.
**(NS*): Group-by-covariate interaction (p≤0.05); marginally significant when interaction is deleted; refer to Appendix O-2 for further analysis of this interaction.
**** Group-by-covariate interaction (p≤0.01); refer to Appendix 0-2 for further analysis of this interaction.
Note: A capital "NS" denotes a relative risk 1.00 or greater for discrete analysis or difference of means nonnegative for continuous analysis; a lower case "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis.

Table 19-33.
Summary of Initial Dioxin Analyses (Model 2) for Immunology Variables (Ranch Hands Only)

Variable	Unadjusted	Adjusted
Physical Examination		
Composite Skin Test Diagnosis (D)	ns	ns
Laboratory: Cell Surface Markers		
CD3 Cells (C)	NS	**(ns)
CD4 Cells (C)	NS	ns
CD5 Cells (C)	NS	**(ns)
CD8 Cells (C)	NS	****
CD14 Cells (C)	NS	NS
CD16+56 Cells (C)	ns	**(NS)
CD20 Cells (C)	NS*	**(ns)
CD25 Cells (C)	NS	ns
CD4-CD8 Ratio (C)	NS	ns
Doubled Labelled Cells: CD3 with CD25 (C)	NS	ns
Doubled Labelled Cells: CD5 with CD20 (D: Zero vs. Nonzero)	ns	ns*
Doubled Labelled Cells: CD5 with CD20 (C: Nonzero Measurements)	NS	ns
Doubled Labelled Cells: CD4 with CD8 (D: Zero vs. Nonzero)	ns	**(ns)
Doubled Labelled Cells: CD4 with CD8 (C: Nonzero Measurements)	NS	**(NS)
Doubled Labelled Cells: CD3 with CD16+56 (D: Zero vs. Nonzero)	NS*	****
Doubled Labelled Cells: CD3 with CD16+56 (C: Nonzero Measurements)	ns*	ns
Laboratory: TLC		
TLC (C)	NS	****
Laboratory: Immunoglobulins		
IgA (C)	NS	NS*
IgG (C)	NS	ns
IgM (C)	NS	NS

Table 19-33. (Continued)
Summary of Initial Dioxin Analyses (Model 2) for Immunology Variables
(Ranch Hands Only)

Variable	Unadjusted	Adjusted
Laboratory:		
Lupus Panel		
ANA Test (D)	ns	NS
Thyroid Microsomal Antibody (D)	ns	**(ns)
MSK Smooth Muscle Antibody (D)	-0.035	-0.022
MSK Mitochondrial Antibody (D)	-0.030	--
MSK Parietal Antibody (D)	ns	ns
Rheumatoid Factor (D)	-0.028	**(ns*)
B Cell Clones Detected by Serum Protein Electrophoresis (D)	NS	NS
Other Antibodies (ANA and MSK) (D)	NS	NS
Summary Index (D)	ns*	ns

C: Continuous analysis.
D: Discrete analysis.
-: Relative risk < 1.00 for discrete analysis.
--: Analysis not performed due to sparse number of abnormalities.
NS or ns: Not significant ($p>0.10$).
NS* or ns*: Marginally significant ($0.05<p\leq0.10$).
**(NS) or **(ns): Log_2 (initial dioxin)-by-covariate interaction ($p\leq0.05$); not significant when interaction is deleted; refer to Appendix O-2 for further analysis of this interaction.
**(ns*): Log_2 (initial dioxin)-by-covariate interaction ($p\leq0.05$); marginally significant when interaction is deleted; refer to Appendix O-2 for further analysis of this interaction.
**** Log_2 (initial dioxin)-by-covariate interaction ($p\leq0.01$); refer to Appendix O-2 for further analysis of this interaction.
Note: P-value given if $p\leq0.05$.
A capital "NS" denotes a relative risk 1.00 or greater for discrete analysis or slope nonnegative for continuous analysis; a lower case "ns" denotes relative risk less than 1.00 for discrete analysis or slope negative for continuous analysis.

Table 19-34.
Summary of Categorized Dioxin Analyses (Model 3) for Immunology Variables (Ranch Hands vs. Comparisons)

Variable	UNADJUSTED			
	Background Ranch Hands vs. Comparisons	Low Ranch Hands vs. Comparisons	High Ranch Hands vs. Comparisons	Low plus High Ranch Hands vs. Comparisons
Physical Examination				
Composite Skin Test Diagnosis (D)	+0.024	NS	ns	NS
Laboratory: Cell Surface Markers				
CD3 Cells (C)	NS	ns	NS	NS
CD4 Cells (C)	NS	ns	NS	NS
CD5 Cells (C)	NS	ns	NS	NS
CD8 Cells (C)	NS	ns	ns	ns
CD14 Cells (C)	NS	-0.033	ns	ns*
CD16+56 Cells (C)	ns	ns	ns	ns
CD20 Cells (C)	NS	ns	NS	NS
CD25 Cells (C)	NS	ns	NS	NS
CD4-CD8 Ratio (C)	NS	NS	NS	NS
Double Labelled Cells: CD3 with CD25 (C)	NS	NS	NS	NS
Double Labelled Cells: CD5 with CD20 (D: Zero vs. Nonzero)	ns	NS	ns	NS
Double Labelled Cells: CD5 with CD20 (C: Nonzero Measurements)	ns	NS	NS*	NS
Double Labelled Cells: CD4 with CD8 (D: Zero vs. Nonzero)	NS	NS	NS	NS
Double Labelled Cells: CD4 with CD8 (C: Nonzero Measurements)	NS	ns	ns	ns
Double Labelled Cells: CD3 with CD16+56 (D: Zero vs. Nonzero)	ns	ns	NS	NS
Double Labelled Cells: CD3 with CD16+56 (C: Nonzero Measurements)	NS	NS	ns	ns
Laboratory: TLC				
TLC (C)	NS	ns	NS	ns

Table 19-34. (Continued)
Summary of Categorized Dioxin Analyses (Model 3) for Immunology Variables (Ranch Hands vs. Comparisons)

Variable	UNADJUSTED			
	Background Ranch Hands vs. Comparisons	Low Ranch Hands vs. Comparisons	High Ranch Hands vs. Comparisons	Low plus High Ranch Hands vs. Comparisons
Laboratory: Immunoglobulins				
IgA (C)	ns	ns	ns	ns
IgG (C)	ns	ns	ns	ns
IgM (C)	NS	ns	ns	ns
Laboratory: Lupus Panel				
ANA Test (D)	ns	ns	-0.030	-0.047
Thyroid Microsomal Antibody (D)	NS	+0.020	NS	+0.016
MSK Smooth Muscle Antibody (D)	NS	NS	ns*	ns
MSK Mitochondrial Antibody (D)	NS	NS	--	ns
MSK Parietal Antibody (D)	ns	NS	ns	NS
Rheumatoid Factor (D)	ns	NS	-0.012	ns
B Cell Clones Detected by Serum Protein Electrophoresis (D)	NS*	ns	NS	ns
Other Antibodies (ANA and MSK) (D)	ns	ns	ns	ns
Summary Index (D)	ns	ns	-0.002	-0.021

C: Continuous analysis.
D: Discrete analysis.
+: Difference of means nonnegative for continuous analysis.
-: Relative risk < 1.00 for discrete analysis or difference of means negative for continuous analysis.
--: Analysis not presented due to sparse number of abnormalities.
NS or ns: Not significant ($p > 0.10$).
NS* or ns*: Marginally significant ($0.05 < p \leq 0.10$).
Note: P-value given if $p \leq 0.05$.
A capital "NS" denotes a relative risk 1.00 or greater for discrete analysis or difference of means nonnegative for continuous analysis; a lower case "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis.

Table 19-34. (Continued)
Summary of Categorized Dioxin Analyses (Model 3) for Immunology Variables (Ranch Hands vs. Comparisons)

Variable	ADJUSTED			
	Background Ranch Hands vs. Comparisons	Low Ranch Hands vs. Comparisons	High Ranch Hands vs. Comparisons	Low plus High Ranch Hands vs. Comparisons
Physical Examination				
Composite Skin Test Diagnosis (D)	**(+0.047)	**(NS)	**(ns)	**(NS)
Laboratory: Cell Surface Markers				
CD3 Cells (C)	**(NS)	**(ns)	**(NS)	**(NS)
CD4 Cells (C)	**(NS)	**(ns)	**(NS)	**(NS)
CD5 Cells (C)	**(NS)	**(ns)	**(NS)	**(NS)
CD8 Cells (C)	**(NS)	**(ns)	**(ns)	**(ns)
CD14 Cells (C)	****	****	****	****
CD16+56 Cells (C)	**(ns)	**(ns*)	**(ns)	**(ns*)
CD20 Cells (C)	+0.013	NS	NS	NS
CD25 Cells (C)	**(NS)	**(ns)	**(NS)	**(NS)
CD4-CD8 Ratio (C)	NS	NS	NS	NS*
Double Labelled Cells: CD3 with CD25 (C)	**(NS)	**(ns)	**(NS)	**(NS)
Double Labelled Cells: CD5 with CD20 (D: Zero vs. Nonzero)	ns	NS	NS	NS
Double Labelled Cells: CD5 with CD20 (C: Nonzero Measurements)	NS	NS	NS	NS
Double Labelled Cells: CD4 with CD8 (D: Zero vs. Nonzero)	NS	NS	ns	NS
Double Labelled Cells: CD4 with CD8 (C: Nonzero Measurements)	**(NS)	**(ns)	**(ns)	**(ns)
Double Labelled Cells: CD3 with CD16+56 (D: Zero vs. Nonzero)	ns	ns	NS	NS
Double Labelled Cells: CD3 with CD16+56 (C: Nonzero Measurements)	NS	NS	ns	ns
Laboratory: TLC				
TLC (C)	**(NS)	**(ns)	**(NS)	**(ns)

Table 19-34. (Continued)
Summary of Categorized Dioxin Analyses (Model 3) for Immunology Variables (Ranch Hands vs. Comparisons)

Variable	ADJUSTED			
	Background Ranch Hands vs. Comparisons	Low Ranch Hands vs. Comparisons	High Ranch Hands vs. Comparisons	Low plus High Ranch Hands vs. Comparisons
Laboratory: Immunoglobulins				
IgA (C)	**(ns)	**(ns)	**(ns)	**(ns)
IgG (C)	**(ns)	**(ns)	**(ns)	**(ns*)
IgM (C)	****	****	****	****
Laboratory: Lupus Panel				
ANA Test (D)	****	****	****	****
Thyroid Microsomal Antibody (D)	****	****	****	****
MSK Smooth Muscle Antibody (D)	NS	NS	ns	ns
MSK Mitochondrial Antibody (D)	--	--	--	--
MSK Parietal Antibody (D)	ns	NS	NS	NS
Rheumatoid Factor (D)	**(ns)	**(NS)	**(-0.035)	**(ns)
B Cell Clones Detected by Serum Protein Electrophoresis (D)	NS	ns	NS	ns
Other Antibodies (ANA and MSK) (D)	ns	ns	ns	ns
Summary Index (D)	ns	ns	-0.019	-0.040

C: Continuous analysis.
D: Discrete analysis.
+: Relative risk $\geq$ 1.00 for discrete analysis or difference of means nonnegative for continuous analysis.
-: Relative risk < 1.00 for discrete analysis.
--: Analysis not performed due to sparse number of abnormalities.
NS or ns: Not significant ($p>0.10$).
NS*: Marginally significant ($0.05<p\leq0.10$).
**(NS) or **(ns*): Categorized dioxin-by-covariate interaction ($p\leq0.05$); not significant when interaction is deleted; refer to Appendix O-2 for further analysis of this interaction.
**(ns*): Categorized dioxin-by-covariate interaction ($p\leq0.05$); marginally significant when interaction is deleted; refer to Appendix O-2 for further analysis of this interaction.
**(0.035): Categorized dioxin-by-covariate interaction ($p\leq0.05$); significant ($p=0.035$) when interaction is deleted; refer to Appendix O-2 for further analysis of this interaction.
**** Categorized dioxin-by-covariate interaction ($p\leq0.01$); refer to Appendix O-2 for further analysis of this interaction.
Note: P-value given if $p\leq0.05$.
A capital "NS" denotes a relative risk 1.00 or greater for discrete analysis or difference of means nonnegative for continuous analysis; a lower case "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis.

Table 19-35.
Summary of Current Dioxin Analyses (Models 4, 5, and 6) for Immunology Variables (Ranch Hands Only)

Variable	UNADJUSTED		
	Model 4: Lipid-Adjusted Current Dioxin	Model 5: Whole-Weight Current Dioxin	Model 6: Whole-Weight Current Dioxin Adjusted for Total Lipids
Physical Examination			
Composite Skin Test Diagnosis (D)	-0.008	-0.012	-0.014
Laboratory: Surface Cell Markers			
CD3 Cells (C)	ns	ns	ns
CD4 Cells (C)	NS	NS	ns
CD5 Cells (C)	NS	NS	ns
CD8 Cells (C)	ns	ns	ns
CD14 Cells (C)	ns	NS	ns
CD16+56 Cells (C)	ns	ns	ns
CD20 Cells (C)	NS	NS	NS
CD25 Cells (C)	ns	ns	ns
CD4-CD8 Ratio (C)	NS	NS	NS
Double Labelled Cells: CD3 with CD25 (C)	ns	ns	ns
Double Labelled Cells: CD5 with CD20 (D: Zero vs. Nonzero)	NS	NS	NS
Double Labelled Cells: CD5 with CD20 (C: Nonzero Measurements)	+0.017	+0.016	+0.044
Double Labelled Cells: CD4 with CD8 (D: Zero vs. Nonzero)	NS	NS	NS
Double Labelled Cells: CD4 with CD8 (C: Nonzero Measurements)	ns	ns	ns
Double Labelled Cells: CD3 with CD16+56 (D: Zero vs. Nonzero)	+0.024	+0.010	+0.042
Double Labelled Cells: CD3 with CD16+56 (C: Nonzero Measurements)	-0.014	-0.009	ns*
Laboratory: TLC			
TLC (C)	NS	NS	ns
Laboratory: Immunoglobulins			
IgA (C)	NS	NS	NS*
IgG (C)	NS	ns	NS
IgM (C)	NS	ns	NS

Table 19-35. (Continued)
Summary of Current Dioxin Analyses (Models 4, 5, and 6) for Immunology Variables (Ranch Hands Only)

Variable	UNADJUSTED		
	Model 4: Lipid-Adjusted Current Dioxin	Model 5: Whole-Weight Current Dioxin	Model 6: Whole-Weight Current Dioxin Adjusted for Total Lipids
Laboratory: **Lupus Panel**			
ANA Test (D)	ns	ns	ns*
Thyroid Microsomal Antibody (D)	NS	NS	NS
MSK Smooth Muscle Antibody (D)	ns*	ns	ns*
MSK Mitochondrial Antibody (D)	ns	ns	ns
MSK Parietal Antibody (D)	NS	NS	NS
Rheumatoid Factor (D)	-0.038	-0.023	ns
B Cell Clones Detected by Serum Protein Electrophoresis (D)	ns	ns	ns
Other Antibodies (ANA and MSK) (D)	NS	NS	NS
Summary Index (D)	-0.028	-0.042	-0.030

C: Continuous analysis.
D: Discrete analysis.
+: Relative risk ≥ 1.00 for discrete analysis or slope nonnegative for continuous analysis.
-: Relative risk < 1.00 for discrete analysis or slope negative for continuous analysis.
NS or ns: Not significant ($p>0.10$).
NS* or ns*: Marginally significant ($0.05<p\leq0.10$).
Note: P-value given if $p\leq0.05$.
A capital "NS" denotes a relative risk of 1.00 or greater for discrete analysis or slope nonnegative for continuous analysis; a lower case "ns" denotes relative risk less than 1.00 for discrete analysis or slope negative for continuous analysis.

Table 19-35. (Continued)
Summary of Current Dioxin Analyses (Models 4, 5, and 6) for Immunology Variables (Ranch Hands Only)

Variable	ADJUSTED		
	Model 4: Lipid-Adjusted Current Dioxin	Model 5: Whole-Weight Current Dioxin	Model 6: Whole-Weight Current Dioxin Adjusted for Total Lipids
Physical Examination			
Composite Skin Test Diagnosis (D)	-0.029	-0.037	**(-0.047)
Laboratory: Surface Cell Markers			
CD3 Cells (C)	ns	NS	ns
CD4 Cells (C)	NS	NS	ns
CD5 Cells (C)	NS	NS	ns
CD8 Cells (C)	**(ns)	ns	ns
CD14 Cells (C)	ns	NS	ns
CD16+56 Cells (C)	NS	ns	NS
CD20 Cells (C)	NS	NS	NS
CD25 Cells (C)	ns	NS	**(ns)
CD4-CD8 Ratio (C)	NS	NS	ns
Double Labelled Cells: CD3 with CD25 (C)	ns	NS	**(ns)
Double Labelled Cells: CD5 with CD20 (D: Zero vs. Nonzero)	NS	NS	NS
Double Labelled Cells: CD5 with CD20 (C: Nonzero Measurements)	NS*	+0.044	NS
Double Labelled Cells: CD4 with CD8 (D: Zero vs. Nonzero)	ns	ns	ns
Double Labelled Cells: CD4 with CD8 (C: Nonzero Measurements)	ns	NS	ns
Double Labelled Cells: CD3 with CD16+56 (D: Zero vs. Nonzero)	****	****	****
Double Labelled Cells: CD3 with CD16+56 (C: Nonzero Measurements)	-0.040	-0.032	ns
Laboratory: TLC			
TLC (C)	NS	NS	NS
Laboratory: Immunoglobulins			
IgA (C)	NS	NS	NS
IgG (C)	ns	ns	ns
IgM (C)	**(ns)	ns	NS

Table 19-35. (Continued)
Summary of Current Dioxin Analyses (Models 4, 5, and 6) for Immunology Variables (Ranch Hands Only)

	ADJUSTED		
Variable	Model 4: Lipid-Adjusted Current Dioxin	Model 5: Whole-Weight Current Dioxin	Model 6: Whole-Weight Current Dioxin Adjusted for Total Lipids
Laboratory: **Lupus Panel**			
ANA Test (D)	**(ns)	**(ns)	**(ns)
Thyroid Microsomal Antibody (D)	**(NS)	NS	NS
MSK Smooth Muscle Antibody (D)	ns	ns	ns
MSK Mitochondrial Antibody (D)	--	--	--
MSK Parietal Antibody (D)	NS	NS	NS
Rheumatoid Factor (D)	-0.013	-0.008	ns*
B Cell Clones Detected by Serum Protein Electrophoresis (D)	ns	**(ns)	**(ns)
Other Antibodies (ANA and MSK) (D)	NS	NS	**(NS)
Summary Index (D)	ns	ns	ns

C: Continuous analysis.
D: Discrete analysis.
+: Slope nonnegative for continuous analysis.
-: Relative risk < 1.00 for discrete analysis or slope negative for continuous analysis.
--: Analysis not performed due to sparse number of abnormalities.
NS or ns: Not significant ($p>0.10$).
NS* or ns*: Marginally significant ($0.05<p\leq 0.10$).
**(NS) or **(ns): Log_2 (current dioxin + 1)-by-covariate interaction ($p\leq0.05$); not significant when interaction is deleted; refer to Appendix O-2 for further analysis of this interaction.
**(0.047): Log_2 (current dioxin + 1)-by-covariate interaction ($p\leq0.05$); significant ($p=0.047$) when interaction is deleted; refer to Appendix O-2 for further analysis of this interaction.
**** Log_2 (current dioxin + 1)-by-covariate interaction ($p\leq0.01$); refer to Appendix O-2 for a detailed description of this interaction.
Note: P-value given if $p\leq0.05$.
A capital "NS" denotes a relative risk of 1.00 or greater for discrete analysis or a nonnegative slope for continuous analysis; a lower case "ns" denotes relative risk less than 1.00 for discrete analysis or slope negative for continuous analysis.

Table 19-36.
Summary of Group-by-Covariate and Dioxin-by-Covariate Interactions from Adjusted Analyses of Immunology Variables

Model	Variable	Covariate
1[a]	CD14 Cells	Occupation
	CD20 Cells	Lifetime Alcohol History
	CD25 Cells	Occupation
	CD4-CD8 Ratio	Physical Activity Index
	Double Labelled Cells: CD3 with CD25 Cells	Occupation
	IgM	Race, Physical Activity Index
	Lupus Panel: Thyroid Microsomal Antibody	Current Cigarette Smoking, Current Alcohol Use, Lifetime Alcohol History
	Lupus Panel: Parietal Antibody	Race
2[b]	CD3 Cells	Occupation
	CD5 Cells	Occupation
	CD8 Cells	Occupation
	CD16+56 Cells	Occupation, Physical Activity Index
	CD20 Cells	Age
	Double Labelled Cells: CD4 with CD8 (D: Zero vs. Nonzero)	Race, Current Cigarette Smoking
	Double Labelled Cells: CD4 with CD8 (C: Nonzero Measurements)	Lifetime Alcohol History
	Double Labelled Cells: CD3 with CD16+56 (D: Zero vs. Nonzero)	Occupation
	TLC	Physical Activity Index
	Lupus Panel: Thyroid Microsomal Antibody	Current Cigarette Smoking, Lifetime Alcohol History
	Lupus Panel: Rheumatoid Factor	Age, Occupation
3[c]	Composite Skin Test Diagnosis	Current Alcohol Use
	CD3 Cells	Age, Occupation
	CD4 Cells	Age, Occupation
	CD5 Cells	Age, Occupation
	CD8 Cells	Age, Occupation
	CD14 Cells	Age
	CD16+56 Cells	Occupation, Lifetime Alcohol History, Physical Activity Index
	CD25 Cells	Age, Occupation, Lifetime Cigarette Smoking History, Lifetime Alcohol History

Table 19-36. (Continued)
Summary of Group-by-Covariate and Dioxin-by-Covariate Interactions from Adjusted Analyses of Immunology Variables

Model	Variable	Covariate
3[c]	Double Labelled Cells: CD3 with CD25 Cells	Occupation, Lifetime Cigarette Smoking History, Lifetime Alcohol History
	CD4 with CD8 (C: Nonzero Measurements)	Age, Race, Occupation
	TLC	Age
	IgA	Race
	IgG	Occupation
	IgM	Physical Activity Index
	Lupus Panel: Antinuclear Antibody (ANA)	Lifetime Alcohol History
	Lupus Panel: Thyroid Microsomal Antibody	Current Cigarette Smoking, Current Alcohol Use, Lifetime Alcohol History
	Lupus Panel: Rheumatoid Factor	Occupation, Physical Activity Index
4[d]	CD8 Cells	Occupation
	Double Labelled Cells: CD3 with CD16+56 (D: Zero vs. Nonzero)	Physical Activity Index
	IgM	Current Alcohol Use
	Lupus Panel: Antinuclear Antibody (ANA)	Race, Lifetime Alcohol History
	Lupus Panel: Thyroid Microsomal Antibody	Current Alcohol Use
5[e]	Double Labelled Cells: CD3 with CD16+56 (D: Zero vs. Nonzero)	Physical Activity Index
	Lupus Panel: Antinuclear Antibody (ANA)	Race, Lifetime Alcohol History
	Lupus Panel: B Cell Clones Detected by Serum Protein Electrophoresis	Current Alcohol Use
6[f]	Composite Skin Test Diagnosis	Occupation
	CD25 Cells	Lifetime Cigarette Smoking History
	Double Labelled Cells: CD3 with CD25 Cells	Lifetime Cigarette Smoking History
	Double Labelled Cells: CD3 with CD16+56 (D: Zero vs. Nonzero)	Physical Activity Index
	Lupus Panel: Antinuclear Antibody (ANA)	Race, Lifetime Alcohol History
	Lupus Panel: B Cell Clones Detected by Serum Protein Electrophoresis	Current Alcohol Use
	Lupus Panel: Other Antibodies (ANA and MSK)	Race

C: Continuous analysis.
D: Discrete analysis.

[a] Group Analysis (Ranch Hands vs. Comparison).
[b] Ranch Hands—Log_2 (Initial Dioxin).
[c] Categorized Dioxin.
[d] Ranch Hands—Log_2 (Current Lipid-Adjusted Dioxin + 1).
[e] Ranch Hands—Log_2 (Current Whole-Weight Dioxin + 1).
[f] Ranch Hands—Log_2 (Current Whole-Weight Dioxin + 1), Adjusted for Total Lipids.

than the enlisted flyer Comparisons. The enlisted groundcrew Ranch Hands had a marginally significantly lower percentage of positive lupus panel ANA test findings than the enlisted groundcrew Comparisons.

Model 2: Initial Dioxin Analyses

In the unadjusted analysis of Model 2, marginally significant positive associations with initial dioxin were revealed for CD20 cells and the CD3 with CD16+56 double labelled cells when dichotomized as zero and nonzero. Significant or marginally significant inverse associations with initial dioxin were revealed for the MSK smooth muscle antibody, the lupus panel rheumatoid factor, the lupus panel summary index, and the analysis of nonzero measurements of CD3 with CD16+56 double labelled cells. The adjusted analysis revealed significant or marginally significant inverse associations between initial dioxin and MSK smooth muscle antibody, rheumatoid factor, and the discretized form (zero vs. nonzero) of CD5 with CD20 double labelled cells. A significant positive association between initial dioxin and IgA was revealed in the adjusted analysis.

Model 3: Categorized Dioxin Analyses

In Model 3, the unadjusted analyses of composite skin test diagnosis and B cell clones each revealed a significantly higher percentage of abnormalities in the background Ranch Hands than the Comparisons. The unadjusted analysis of CD14 cells showed the low Ranch Hands to have significantly lower mean CD14 cell counts than the Comparisons. However, the lupus panel thyroid microsomal antibody test showed the low Ranch Hands to have significantly higher positive findings than the Comparisons. A significantly or marginally significantly lower percentage of abnormalities were noted in the high Ranch Hands than the Comparisons for the lupus panel ANA test, MSK smooth muscle antibody, rheumatoid factor, and the lupus panel summary index. The high Ranch Hands exhibited a higher mean value than the Comparisons for the double labelled cells CD5 with CD20 for measurements above zero. The unadjusted analysis revealed significantly or marginally significantly lower values for the low plus high Ranch Hands than the Comparisons for CD14 cells, the lupus panel ANA test, and the lupus panel summary index. The low plus high Ranch Hands exhibited a significantly higher percentage of positive results for the lupus panel thyroid microsomal antibody than the Comparisons.

The adjusted analysis of Model 3 revealed a significantly higher percentage of composite skin test abnormalities in the background Ranch Hands than the Comparisons. Similarly, the mean CD20 cell count was higher in the background Ranch Hands than the Comparisons. The adjusted analysis of Model 3 revealed marginally significantly lower mean CD16+56 cell values in the low Ranch Hands than the Comparisons. The lupus panel rheumatoid factor test and the lupus panel summary index each showed a significantly lower percentage of positive findings in the high Ranch Hands than the Comparisons. The adjusted analysis of CD15+56 cells and immunoglobulin IgG revealed marginally significantly lower means in the low plus high Ranch Hands than the Comparisons. The percentage of abnormalities in the lupus panel summary index was significantly lower in the low plus high Ranch Hands than the Comparisons. A marginally significantly higher mean CD4 to CD8 ratio existed in the low plus high Ranch Hands than the Comparisons.

Models 4, 5, and 6: Current Dioxin Analyses

The unadjusted analysis of Models 4, 5, and 6 revealed significant or marginally significant inverse associations between current dioxin and composite skin test diagnosis, CD3 with CD16+56 double labelled cells with measurements above zero, and the lupus panel summary index. The unadjusted analysis of Models 4 through 6 showed positive relationships between current dioxin and the double labelled cells CD5 with CD20 with measurements above zero and the double labelled cells CD3 with CD16 with values dichotomized as zero and nonzero. The unadjusted analysis of Model 4 showed marginally significant or significant inverse associations with the lupus panel MSK smooth muscle antibody and rheumatoid factor. The lupus panel rheumatoid factor was inversely associated with current dioxin in Model 5. The unadjusted analysis for Model 6 revealed a marginally significant positive association between current dioxin and the immunoglobulin IgA. Model 6 also showed a marginally significant inverse relationship between current dioxin and the lupus panel ANA test and MSK smooth muscle antibody.

In the adjusted analysis of each of Models 4 through 6, the composite skin test diagnosis and lupus panel rheumatoid factor showed significant or marginally significant inverse relationships with current dioxin. In the adjusted analysis of Models 4 and 5, the nonzero double labelled cells CD5 with CD20 measurements showed a marginally significant or significant increase with current dioxin. The double labelled cells CD3 with CD16+56 for measurements above zero also displayed significant inverse relationships with current dioxin in Models 4 and 5.

CONCLUSION

In general, the composite skin test diagnosis results did not differ significantly between Ranch Hands and Comparisons and were not positively associated with initial or current dioxin levels. For the most part, the cell surface marker variables and total lymphocyte count did not display significant associations with serum dioxin. The longitudinal analyses of the CD4-CD8 ratio did not consistently show significant differences between the 1992 ratio relative to the 1985 measurement of the ratio.

Marginally significant positive associations were found between IgA and initial dioxin. A negative association would be expected in immunologic deficiency; however, the increased IgA levels could represent a chronic inflammatory response to dioxin exposure and thus suggest long-term evaluation.

The statistically significant inverse relationships revealed between dioxin and a few of the lupus panel autoantibodies also are inconsistent with a harmful effect from dioxin. The presence of these autoantibodies, such as MSK smooth muscle antibody, rheumatoid factor, and the lupus panel summary index, is generally considered to be abnormal. However, the presence of fewer than expected of these autoantibodies also may be abnormal. This may suggest a possible early immune alteration that may not carry clinical significance. These findings should be investigated and clarified in further followups.

The indices of immune responses analyzed in this chapter provided a comprehensive reflection of in vivo and in vitro immune function in the study population. No clinically significant indicators reflecting a consistent relationship between serum dioxin and deficiency in immune function were found.

CHAPTER 19
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CHAPTER 20
PULMONARY ASSESSMENT

INTRODUCTION

Background

Apart from local irritative symptoms occurring in industrial accidents, there is no clinical evidence that the human lung is a target organ for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, or dioxin) toxicity. A single case of hypersensitivity pneumonitis was described in a Vietnam veteran occupationally exposed to herbicides (1), though there was no scientific basis to support a causal relationship to TCDD. The respiratory failure that has been reported in rare cases of extreme phenoxy herbicide intoxication appears to be related to central nervous system depression rather than primary pneumotoxicity (2,3).

Research into the pulmonary toxicity of dioxin in laboratory animals has focused on the physicochemical properties of the cytosolic aryl hydrocarbon (Ah) receptor and the cytochrome P-450 enzyme system in mice (4), rats (5,6), and rabbits (7-11).

Several lines of research have heightened interest in the possibility that TCDD might cause pneumotoxicity in man. In one study (12), cytosol preparations were examined from human lung tissue specimens obtained at surgery. Only 10 of 53 specimens had detectable Ah receptors, and those were at concentrations far less (10% to 30%) than those found in lung cytosols from laboratory animals. In mice, the induction of cytochrome P-450 enzymes by TCDD in lung was found to be similar to that in liver (13). In rats (14,15), the intratracheal administration of TCDD was associated with significant dose-related increases in hepatic enzymes as well, establishing the transpulmonary absorption of dioxin and hence, the potential for pneumotoxicity.

Lung disease has been included infrequently as a clinical endpoint in epidemiologic studies of humans exposed to phenoxy herbicides. In one report (16), standard pulmonary function tests were included in clinical examinations of 367 employees 30 years after an industrial explosion associated with high-level exposure to 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and, by contamination, to TCDD. Although tissue levels were not available, 55 percent of the exposed cohorts developed chloracne, testimony of the severity of exposure. Alone among the objective laboratory indices, pulmonary function as assessed by the forced expiratory volume, expelled at 1 second (FEV_1) percent-predicted values was significantly ($p=0.0005$) compromised in the exposed cohort of current smokers but not in former smokers or in those who had never smoked.

In a more recent report (17), the authors investigated the prevalence of chronic respiratory disease in a cohort of 281 workers occupationally exposed to TCDD in chemical factories. The body burden of dioxin was objectively determined by serum TCDD levels with a mean level of 220 ppt in the exposed cohort versus 7 ppt in the controls. No significant differences were documented in the historical incidence of respiratory disease or in the standard indices of lung function in the exposed cohort relative to the controls. In the

most recent reports of the Air Force Health Study (AFHS) (18,19), no significant differences were found between the Ranch Hand and Comparison cohorts in most historical, physical examination, and pulmonary function indices. As a non-specific exception, in the 1987 serum dioxin study, for a physical examination variable thorax and lung abnormalities, Ranch Hands in the low and high current dioxin categories exhibited higher percentages of abnormalities than Comparisons.

Although several animal experiments have documented the occurrence of lung cancers associated with TCDD toxicity in rats (20) and in mice (21), several large-scale epidemiologic studies in humans exposed occupationally (22,23), as a consequence of industrial accidents (24,25), or by military service (18,19,26-28) found no increase in the occurrence of lung cancer in populations at risk. In one report, Marine Vietnam veterans were found to be at increased risk for the development of lung cancer (29). A more recent proportionate mortality study conducted by the Veterans' Administration reviewed the data and concluded that the apparent increased risk might have been related to a lower than expected mortality from lung cancer in the control group of Marines that did not serve in Vietnam (30).

Summary of Previous Analyses of the Air Force Health Study

1982 Baseline Study Summary Results

The 1982 Baseline examination explored historical pulmonary disease by questionnaire and active pulmonary function by standardized spirometric technique. These areas were of significant interest because of suggested operational inhalation of Herbicide Orange by all Ranch Hand enlisted flyers and enlisted groundcrew.

The questionnaire revealed no group differences for historical diagnoses of tuberculosis and fungal infections, pneumonia, cancer, or chronic sinusitis and upper respiratory disease. At the physical examination, the unadjusted means for FEV_1 (percent predicted), forced vital capacity (FVC), and the ratio of FEV_1 to FVC were almost identical between Ranch Hands and Comparisons. Adjusted mean values were not calculated due to significant interactions (group-by-age for FEV_1 and FVC, group-by-smoking for the ratio of FEV_1 to FVC).

Detailed exposure analyses showed two significant associations in the enlisted flyer and enlisted groundcrew strata, but neither was indicative of a linear dose response. Attempts to adjust the means of the pulmonary function values for age and smoking revealed several interactions, but results were essentially negative. Overall, there were no pulmonary diseases, pulmonary function data, or associations of concern.

1985 Followup Study Summary Results

Because of the essentially negative pulmonary analyses from the Baseline examination, pulmonary function (spirometric) studies were not performed during the 1985 followup examination. Collection of pulmonary data was limited to a questionnaire history of respiratory disease, physical examination of the thorax and lungs, and pulmonary

abnormalities detected on a routine chest x ray. Mortality due to respiratory disease also was evaluated.

There were no significant group differences found for reported history of asthma, bronchitis, pleurisy, or tuberculosis based on the unadjusted analyses. Adjustments for age and lifetime smoking did not alter the findings of group similarity, although there was a significant group-by-lifetime smoking interaction for pleurisy and tuberculosis.

Similarly, there were no significant group differences in the unadjusted analyses for the radiological and clinical respiratory findings of thorax and lungs, asymmetrical expansion, hyperresonance, dullness, wheezes, rales, and x ray interpretations. These findings were supported by the adjusted analyses, although there was a group-by-age interaction for rales. Also, the exposure index analyses revealed no consistent dose-response pattern.

1987 Followup Study Summary Results

The pulmonary assessment was based on five self-reported respiratory illnesses, seven clinical observations, and eight laboratory measurements. No evidence of an herbicide effect was detected in the assessment of the reported respiratory illnesses. The health of the two groups was reasonably comparable based on the clinical and laboratory variables, although Ranch Hands had a significantly higher percentage of thorax and lung abnormalities on examination than did Comparisons, based on the unadjusted analysis, and a marginally higher percentage after adjustment for covariates. No significant group differences were detected in the adjusted analyses when significant interactions involving group were ignored. Exploration of these group-by-covariate interactions did not reveal a consistent pattern indicating an herbicide effect. The adverse effects of smoking on pulmonary status were evident in all analyses.

Serum Dioxin Analysis of 1987 Followup Study Summary Results

In general, there was no association between initial dioxin and the discrete variables. For the continuous variables, however, there appeared to be a negative association with initial dioxin, especially under the maximal assumption. The associations with current dioxin did not differ significantly between the two time strata for any of the variables, under either assumption. In the categorized current dioxin analyses, the percentage of abnormalities did not differ significantly among the four current dioxin categories for any of the questionnaire and physical examination variables, except under the adjusted analysis of thorax and lung abnormalities. In this case, Ranch Hands in the low and high categories had a higher percentage of abnormalities than did Comparisons in the background category; but Ranch Hands in the unknown category had a lower percentage of abnormalities than did Comparisons in the background category. For the continuous variables, the means differed among the current dioxin categories. For FVC, FEV_1, and forced expiratory flow maximum (FEFmax), the mean for the Ranch Hands in the unknown category tended to be greater than the mean for the Comparisons in the background category, but the means for the low and high categories were less than the mean for the background category. In the analysis of the ratio of observed FEV_1 to observed FVC, this trend was reversed.

In the longitudinal analysis of the ratio of observed FEV_1 to observed FVC, there was a significant positive association with current dioxin and a significant difference among the current dioxin categories.

In summary, the historical, physical examination, and laboratory data analyzed in the 1987 serum dioxin followup study revealed no evidence for an increased occurrence of pulmonary disease in the Ranch Hand cohort in relation to the body burden of dioxin. Analysis of two laboratory variables, FVC and the ratio of observed FEV_1 to observed FVC, yielded results that were consistent with subtle dose-response effects related to the body burden of dioxin in Ranch Hands. Body habitus and, more specifically, percent body fat may play a role in these associations between dioxin and pulmonary function indices.

Parameters for the Pulmonary Assessment

Dependent Variables

The Pulmonary Assessment was based on questionnaire, physical examination, and laboratory data collected at the 1992 followup examination.

Medical Records Data

In the self-administered family and personal history section, each study participant was asked whether he had ever experienced the following conditions: asthma, bronchitis, or pneumonia. This self-reported information was combined with information from the 1992 physical examination, the 1985 and 1987 questionnaires and physical examinations, and the Baseline questionnaire and examination and was subsequently verified by a review of the participant's medical records. These three variables were individually analyzed as measures of the pulmonary health status of each participant. Participants with occurrences of asthma, bronchitis, or pneumonia before duty in SEA were excluded from the analyses of these variables.

Physical Examination Data

Part of the Pulmonary Assessment was based on the results of the physical examination of the thorax and lungs. A composite variable, thorax and lung abnormalities, was constructed based on the presence or absence of asymmetrical expansion, hyperresonance, dullness, wheezes, rales, or chronic obstructive pulmonary disease, as well as the physician's assessment of abnormality. This variable was coded as "abnormal" if any of these conditions were present and "normal" if none of these conditions were present. No participants were excluded for medical reasons from the analysis of this variable.

Laboratory Examination Data

The assessment of the laboratory examination data included the analysis of pulmonary abnormalities detected on a routine chest x ray. This variable was coded as "normal" or "abnormal." The assessment also included the analysis of pulmonary physiologic data collected during the physical examination employing standard spirometric techniques.

Numerous indices were derived including FVC—a measurement of the amount of air in liters expelled from maximum inspiration to full expiration, and FEV_1 in liters—an index derived from the FVC that quantifies the amount of air expelled at 1 second. The values used for these variables were the percentages of predicted values rather than the actual volume or flow rate. The calculations of these percentages included an adjustment for age and height, as prescribed by the American Thoracic Society. The Scripps Clinic and Research Foundation (SCRF) laboratory used the same predictive values regardless of race. For these indices, lower values indicated greater compromise in the lung function. In addition, the ratio of observed FEV_1 to observed FVC was calculated as an index reflective of obstructive airway disease. These variables were analyzed as continuous variables.

Loss of vital capacity and obstructive abnormality were classified as none, mild, moderate, or severe and were analyzed as part of the Pulmonary Assessment. Results judged to be between none and mild were classified as "mild" for all analyses. A similar methodology was used for results between mild and moderate (i.e., classified as "moderate") and between moderate and severe (i.e., classified as "severe"). Due to the low frequencies in the moderate and severe categories, these two categories were combined in the analysis as necessary.

As a guide for determining abnormal pulmonary function, readings below the 95th percentile were considered abnormal for FVC and FEV_1. For men older than 36 years of age, the corresponding percent predicted is 74 percent for the FVC and 73 percent for the FEV_1. An FVC or FEV_1 below 40 percent of that predicted was considered severely impaired, as recommended by the American Thoracic Society. The division between mild, moderate, and severe impairment was arbitrarily defined by dividing the interval between severe impairment and the lower limit of normal into two equal bands. That is, the cutpoint between mild and moderate impairment was at 57 percent of the predicted value. Although the ratio of observed FEV_1 to observed FVC and the appearance of the flow volume curve are useful to the physician interpreting the test, there was insufficient data to support arbitrary lower limits of normal or cutpoints to classify impairment as mild, moderate, or severe.

No participants were excluded for medical reasons from the analysis of these variables.

Covariates

The effects of age, race, military occupation, current cigarette smoking (cigarettes/day), lifetime cigarette smoking history (pack-years), body fat (percent), and exposure to industrial chemicals (yes, no) were used in adjusted statistical analyses evaluating the pulmonary dependent variables. Current cigarette smoking was used as a candidate covariate for the physical examination and laboratory variables. Current cigarette smoking and lifetime cigarette smoking history were based on self-reported questionnaire data. For lifetime cigarette smoking history, the respondent's average smoking was estimated over his lifetime, assuming 365 packs of cigarettes equal 1 pack-year. The exposure to industrial chemicals covariate represented lifetime exposure based on self-reported questionnaire data from this examination combined with previous examinations.

Age, current cigarette smoking, lifetime cigarette smoking history, and body fat were used in the continuous form for modeling purposes in all general linear models and logistic regression analyses. These covariates were discretized for clarity of presentation (e.g., interaction summaries).

Statistical Methods

Chapter 7, Statistical Methods, describes the basic statistical methods used throughout this report. Table 20-1 summarizes the statistical analyses performed for the Pulmonary Assessment. The first part of this table lists the dependent variables analyzed, the source of the data, the form of the data, cutpoints, the candidate covariates, and the statistical methods. The second part of the table further describes the candidate covariates. Abbreviations used in the body of the table are defined at the end of the table. Table 20-2 provides the number of participants with missing dependent variable and covariate data and those excluded due to pre-SEA conditions.

Analyses of data collected at the 1987 followup study indicated that dioxin was associated with military occupation. In general, enlisted personnel had higher levels of dioxin than officers, with enlisted groundcrew having higher levels than enlisted flyers. Consequently, adjustment for military occupation in statistical models using dioxin as a measure of exposure may improperly mask an actual dioxin effect. However, occupation also can be a surrogate for socioeconomic effects. Failure to adjust for occupation could overlook important risk factors related to lifestyle. If occupation was found to be significantly associated with a dependent variable in the 1992 followup analyses and was retained in the final statistical models using dioxin as a measure of exposure, the dioxin effect was evaluated in the context of two models. Analyses were performed with and without occupation in the final models to investigate whether conclusions regarding the association between the health endpoint and dioxin differed.

Similarly, body fat exhibited a significant positive association with dioxin in the serum dioxin analysis of the 1987 followup data. Body fat also was found to be significantly associated with dioxin in the 1992 followup analyses, as discussed in Chapter 9, General Health. Consequently, clinical endpoints in the Pulmonary Assessment may be related to dioxin due to the association between dioxin and body fat. To investigate this possibility, the dioxin effect was evaluated in the context of two models whenever body fat was retained in the final model. Analyses again were performed with and without body fat in the model to investigate whether conclusions regarding the association between the health endpoint and dioxin differed.

The results of the analyses without occupation and body fat in the final adjusted model are presented in Appendix P-3 and are discussed in the text only if the level of significance differs from the original final adjusted model (significant versus nonsignificant).

Longitudinal Analysis

Longitudinal analyses were performed to evaluate associations between exposure and the change in the ratio of observed FEV_1 to observed FVC between the 1982 Baseline examination and the 1992 followup. Chapter 7, Statistical Methods, contains a further discussion of methods used in the longitudinal analysis.

Table 20-1.
Statistical Analyses for the Pulmonary Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analysis
Asthma	MR-V	D	Yes No	AGE,RACE,OCC, PACKYR,BFAT,IC	U:LR,CS A:LR
Bronchitis	MR-V	D	Yes No	AGE,RACE,OCC, PACKYR,BFAT,IC	U:LR,CS A:LR
Pneumonia	MR-V	D	Yes No	AGE,RACE,OCC, PACKYR,BFAT,IC	U:LR,CS A:LR
Thorax and Lung Abnormalities	PE	D	Yes No	AGE,RACE,OCC, CSMOK,PACKYR, BFAT,IC	U:LR,CS A:LR
X Ray Interpretation	LAB	D	Abnormal Normal	AGE,RACE,OCC, CSMOK,PACKYR, BFAT,IC	U:LR,CS A:LR
Forced Vital Capacity (FVC) (percent of predicted)	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, BFAT,IC	U:GLM,TT A:GLM
Forced Expiratory Volume in 1 Second (FEV_1) (percent of predicted)	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, BFAT,IC	U:GLM,TT A:GLM
Ratio of Observed FEV_1 to Observed FVC	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, BFAT,IC	U:GLM,TT A:GLM L:GLM
Loss of Vital Capacity	LAB	D	Moderate or Severe Mild None	AGE,RACE,OCC, CSMOK,PACKYR, BFAT,IC	U:PR,CS A:PR
Obstructive Abnormality	LAB	D	Moderate or Severe Mild None	AGE,RACE,OCC, CSMOK,PACKYR, BFAT,IC	U:PR,CS A:PR

Table 20-1. (Continued)
Statistical Analyses for the Pulmonary Assessment

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Age (AGE)	MIL	D/C	Born≥1942 Born<1942
Race (RACE)	MIL	D	Black Non-Black
Occupation (OCC)	MIL	D	Officer Enlisted Flyer Enlisted Groundcrew
Current Cigarette Smoking (CSMOK) (cigarettes/day)	Q-SR	D/C	0-Never 0-Former >0-20 >20
Lifetime Cigarette Smoking History (PACKYR) (pack-years)	Q-SR	D/C	0 >0-10 >10
Body Fat (BFAT) (percent)	PE	D/C	Lean or Normal: ≤25% Obese: >25%
Industrial Chemicals Exposure (IC)	Q-SR	D	Yes No

Abbreviations

Data Source:
- LAB = 1992 laboratory results
- MIL = Air Force military records
- MR-V = Medical records (verified)
- PE = 1992 physical examination
- Q-SR = Health questionnaires (self-reported)

Data Form:
- C = Continuous analysis only
- D = Discrete analysis only
- D/C = Appropriate form for analysis (either discrete or continuous)

Statistical Analyses:
- U = Unadjusted analyses
- A = Adjusted analyses
- L = Longitudinal analyses

Statistical Methods:
- CS = Chi-square contingency table analysis (continuity-adjusted for 2 × 2 tables)
- GLM = General linear models analysis
- LR = Logistic regression analysis
- PR = Polytomous logistic regression analysis
- TT = Two-sample t-test

Table 20-2.
Number of Participants with Missing Data for, or Excluded from, the Pulmonary Assessment

		Group		Dioxin (Ranch Hands Only)		Categorized Dioxin	
Variable	Variable Use	Ranch Hand	Comparison	Initial	Current	Ranch Hand	Comparison
X Ray Interpretation	DEP	1	0	1	1	1	0
FVC	DEP	1	1	0	1	1	1
FEV_1	DEP	1	1	0	1	1	1
Ratio of Observed FEV_1 to Observed FVC	DEP	1	1	0	1	1	1
Loss of Vital Capacity	DEP	1	1	0	1	1	1
Obstructive Abnormality	DEP	1	1	0	1	1	1
Current Cigarette Smoking	COV	0	2	0	0	0	2
Lifetime Cigarette Smoking History	COV	1	2	0	1	1	2
Pre-SEA Asthma	EXC	10	8	6	10	10	7
Pre-SEA Bronchitis	EXC	26	28	15	25	25	23
Pre-SEA Pneumonia	EXC	49	55	25	49	49	43

Abbreviations: DEP = Dependent variable (missing data).
COV = Covariate (missing data).
EXC = Exclusion.

Note: 952 Ranch Hands and 1,281 Comparisons;
520 Ranch Hands for initial dioxin; 894 Ranch Hands for current dioxin;
894 Ranch Hands and 1,063 Comparisons for categorized dioxin.

One Ranch Hand missing total lipids for current dioxin.

RESULTS

Dependent Variable-Covariate Associations

Results from the tests of association between the pulmonary dependent variables and covariates are presented in Appendix Table P-1-1. These associations are based on combined group data, and participants with pre-SEA duty occurrences of asthma, bronchitis, or pneumonia were excluded from the association analyses of the respective dependent variables.

A statistically significant association was found between post-SEA asthma and lifetime cigarette smoking history ($p=0.049$). A higher percentage of participants with 10 or fewer pack-years had a history of post-SEA asthma (4.6%), as compared to participants who never smoked (2.6%) and participants with more than 10 pack-years (2.6%).

The association between post-SEA bronchitis and lifetime cigarette smoking history also was significant ($p<0.001$). The percentage of participants with a history of bronchitis increased as the number of pack-years increased (0 pack-years: 13.5%, >0-10 pack-years: 16.7%, >10 pack-years: 21.4%). Bronchitis also was significantly associated with industrial chemicals exposure ($p=0.026$). Of participants who reported exposure to industrial chemicals, 19.4 percent had a history of post-SEA bronchitis versus 15.6 percent in participants without reported exposure.

A history of post-SEA pneumonia was found to be significantly associated with age and lifetime cigarette smoking history ($p=0.010$ and $p=0.003$ respectively). Of older participants, 12.1 percent had a history of post-SEA pneumonia versus 8.5 percent of younger participants. A history of pneumonia was more prevalent among participants with greater than 10 pack-years (13.1%) as compared to participants who never smoked (9.4%) and those with 10 or fewer pack-years (8.1%).

Statistically significant associations were found between the occurrence of thorax and lung abnormalities and age, occupation, current cigarette smoking, and lifetime cigarette smoking history ($p<0.001$ for each analysis). Results indicated that the prevalence of thorax and lung abnormalities increased with age, number of cigarettes per day, and number of pack-years. Within the occupation categories, the enlisted flyers exhibited the highest percentage of abnormalities (17.0%) compared to the enlisted groundcrew (13.4%) and officers (8.5%). The highest percentage of abnormalities among all strata of significant covariates occurred in participants who smoke more than 20 cigarettes per day (38.7%). Of interest, over the 10-year course of these examinations, the percentage of participants who currently smoke has steadily decreased from 42 percent in 1982 to 25 percent in 1992.

Association tests for x ray interpretation revealed significant relationships with age and lifetime cigarette smoking history ($p<0.001$ and $p=0.009$ respectively). A higher percentage of older participants (16.1%) than younger participants (10.0%) had an abnormal x ray interpretation. A direct relationship also was found with lifetime cigarette smoking history. The percentage of abnormal x ray interpretations increased with the number of pack-years (0 pack-years: 11.1%, 0-10 pack-years: 12.0%, >10 pack-years: 16.0%).

The following covariates were significantly associated with FVC (percent of predicted): age, race, occupation, current cigarette smoking, lifetime cigarette smoking history, and body fat ($p<0.001$ for all analyses). For age, current cigarette smoking, lifetime cigarette smoking history, and body fat, the association with FVC was inverse in nature such that as the covariate increased, the percent of predicted FVC decreased. The mean percent of predicted FVC was lower for Blacks (88.0) than for non-Blacks (101.1). The means also were lower for enlisted participants (flyers: 99.1, groundcrew: 99.3) than for officers (102.0). For FVC, lower values indicate greater compromise in lung function.

Associations involving FEV_1 (percent of predicted) are similar to the covariate associations involving FVC. All associations between FEV_1 and each of the continuously-scaled covariates were inverse (age: $r=-0.213$, $p<0.001$, current cigarette smoking: $r=-0.210$, $p<0.001$, lifetime cigarette smoking history: $r=-0.295$, $p<0.001$, body fat: $r=-0.048$, $p=0.024$). Non-Blacks exhibited a higher mean FEV_1, (95.5) than Blacks (86.8), and the enlisted flyer mean (91.8) was the lowest of the occupation strata ($p<0.001$ for race and occupation). For FEV_1, lower values indicated an adverse health effect in pulmonary function.

The ratio of observed FEV_1 to observed FVC displayed highly significant covariate associations with age, race, occupation, current cigarette smoking, lifetime cigarette smoking history, and body fat ($p<0.001$ for all analyses). Due to the distribution of the data, a natural logarithm (1-X) transformation was used. Because of this transformation, a negative correlation between the covariate and the transformed variable implies a positive association between the covariate and the ratio of observed FEV_1 to observed FVC and vice versa. Positive correlations were displayed between the transformed variable and age ($r=0.326$), current cigarette smoking ($r=0.192$), and lifetime cigarette smoking history ($r=0.299$). These positive correlations between the covariate and the transformed variable suggest that as the covariate increases, the ratio of FEV_1 to FVC tends to decrease. The association between body fat and the transformed variable was negative ($r=-0.182$) indicating that as body fat increases, the ratio of FEV_1 to FVC also tends to increase. The mean ratio for Blacks (0.797) was higher than for non-Blacks (0.759), and among the occupational strata, the mean ratio was higher for enlisted groundcrew (0.773) than for officers (0.754) and enlisted flyers (0.748). In general, higher values of the ratio of FEV_1 to FVC (approaching 1) are medically preferable. However, if the increase in the ratio is due primarily to the decrease in FVC (the denominator), then the increase in the ratio represents an artificial increase in pulmonary function (which appears to be the case for these data).

Statistically significant associations were found between loss of vital capacity and each of the following covariates: age ($p=0.001$), race ($p<0.001$), current cigarette smoking ($p=0.001$), lifetime cigarette smoking history ($p=0.003$), and body fat ($p=0.001$). Participants born before 1942 exhibited a higher prevalence of loss of vital capacity (mild: 7.4%, moderate or severe: 1.6%) than those born during or after 1942 (mild: 4.2%, moderate or severe: 0.6%). Black participants demonstrated a higher prevalence of loss of vital capacity (mild: 17.6%, moderate or severe: 6.1%) than non-Black participants (mild: 5.3%, moderate or severe: 0.9%). Results also indicate that the prevalence of mild and moderate or severe loss of vital capacity increases as the number of cigarettes per day and number of pack-years increase. Participants in the obese body fat category exhibited higher

prevalences of both mild (8.4%) and moderate or severe (2.1%) losses of vital capacity than participants in the normal or lean category (mild: 5.2%, moderate or severe: 0.9%).

When tested for association, obstructive abnormality was found to be significantly associated with age ($p<0.001$), occupation ($p<0.001$), current and lifetime cigarette smoking ($p<0.001$), and body fat ($p=0.023$). The prevalence of obstructive abnormalities was higher for older participants (mild: 45.6, moderate or severe: 10.3) than for younger participants (mild: 23.8, moderate or severe: 2.7). The enlisted flyers exhibited a higher prevalence of both mild and moderate or severe obstructive abnormalities than the officers and the enlisted groundcrew. Percentages of obstructive abnormalities also increased as the number of cigarettes smoked each day increased and as the number of pack-years increased. The prevalence of obstructive abnormalities was higher for participants with lean or normal body fat (mild: 37.3%, moderate or severe: 7.6%) than for participants in the obese body fat category (mild: 33.2%, moderate or severe: 5.5%).

Exposure Analysis

The following section presents results of the statistical analyses of the dependent variables shown in Table 20-1. Dependent variables are grouped into three sections: those derived and verified from a review of medical records, data obtained during the 1992 physical examination, and data derived from the laboratory portion of the 1992 followup examination.

Unadjusted and adjusted analyses of six models are presented for each variable. Model 1 examines the relationship between the dependent variable and group (Ranch Hand or Comparison). Model 2 explores the relationship between the dependent variable and an extrapolated initial dioxin measure for Ranch Hands who had a 1987 dioxin level greater than 10 ppt. If a participant did not have a 1987 dioxin level, a 1992 level was used. A statistical adjustment for the percent of body fat at the participant's time of duty in SEA and the change in the percent body fat from the time of duty in SEA to the date of the blood draw for dioxin is included in this model to account for body-fat-related differences in elimination rate (31). Model 3 dichotomizes the Ranch Hands in Model 2 based on their initial dioxin measures; these two categories of Ranch Hands are referred to as the "low Ranch Hand" category and the "high Ranch Hand" category. These participants are added to Ranch Hands and Comparisons with current serum dioxin levels (1987, if available; 1992, if the 1987 level was not available) at or below 10 ppt to create a total of four categories. Ranch Hands with current serum dioxin levels at or below 10 ppt are referred to as the "background Ranch Hand" category. The relationship between the dependent variable in each of the three Ranch Hand categories and the dependent variable in the "Comparison" category is examined. A fourth contrast, exploring the relationship of the dependent variable in the low Ranch Hand category and the high Ranch Hand category combined, also is conducted. This combination is referred to in the text and tables as the "low plus high Ranch Hand" category. As in Model 2, a statistical adjustment is made for percent body fat at the participant's time of duty in SEA and the change in the percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

Models 4, 5, and 6 examine the relationship between the dependent variable and 1987 dioxin levels in all Ranch Hands with a dioxin measurement. If a participant did not have a 1987 dioxin measurement, a 1992 measurement was utilized in determining the current dioxin level. The measure of dioxin in Model 4 is lipid-adjusted, whereas whole-weight dioxin is used in Models 5 and 6. Model 6 differs from Model 5 in that a statistical adjustment for total lipids is included in Model 6. Further details on dioxin and the modeling strategy are found in Chapters 2 and 7 respectively.

Results of investigations for group-by-covariate and dioxin-by-covariate interactions are referenced in the text, and tabular results are presented in Appendix P-2. As described previously, additional analyses were performed when occupation or body fat was retained in the final model for Models 2 through 6. Results excluding occupation and body fat from these models are tabled in Appendix P-3, and dioxin-by-covariate interactions with occupation and body fat excluded from these models are presented in Appendix P-4. Results from analyses excluding occupation and body fat are discussed in the text only if a meaningful change in the results occurred (that is, changes between significant results, marginally significant results, and nonsignificant results).

Verified Medical Records Variables

Asthma

The Model 1 unadjusted and adjusted analyses of post-SEA asthma exhibited no significant associations between group and post-SEA asthma (Table 20-3(a,b): $p > 0.12$ for all contrasts). The final adjusted model included significant occupation-by-body fat and age-by-body fat interactions.

Similar to the results for Model 1, the analysis of post-SEA asthma within Models 2 and 3 found no significant results (Table 20-3(c-f): $p \geq 0.15$ for all analyses). The final adjusted model for Model 2 included the significant interactions of age-by-lifetime cigarette smoking history and race-by-body fat. The interactions of age-by-race, race-by-lifetime cigarette smoking history, race-by-body fat, and occupation-by-body fat were significant in the Model 3 final adjusted model.

Current dioxin levels were examined for a significant relationship with post-SEA asthma in Models 4, 5, and 6. All unadjusted analysis results were nonsignificant (Table 20-3(g): $p > 0.61$ for all analyses). Adjusted analyses of Models 4 and 6 revealed a significant current dioxin-by-age interaction (Table 20-3(h): $p = 0.049$ and $p = 0.037$ respectively). Results stratified by age categories are presented in Appendix Table P-2-1. Results for Models 4 and 6 reported in Table 20-3(h) were derived from the final model after deletion of the current dioxin-by-age interaction. No significant associations between the history of asthma and current dioxin were uncovered from the adjusted analyses of Models 4, 5, and 6 (Table 20-3(h): $p > 0.67$ for all contrasts). The interactions of age-by-race and race-by-body fat were significant for Models 4, 5, and 6; occupation-by-body fat was also significant in Model 4, and occupation was significant in Model 5.

Table 20-3.
Analysis of Asthma

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Percent Yes**	**Est. Relative Risk (95% C.I.)**	**p-Value**
All	***Ranch Hand***	***942***	***3.9***	***1.49 (0.93,2.39)***	***0.124***
	Comparison	***1,273***	***2.7***		
Officer	Ranch Hand	364	4.4	1.72 (0.82,3.63)	0.209
	Comparison	500	2.6		
Enlisted Flyer	Ranch Hand	160	1.9	0.95 (0.21,4.29)	0.999
	Comparison	202	2.0		
Enlisted Groundcrew	Ranch Hand	418	4.3	1.47 (0.75,2.88)	0.346
	Comparison	571	3.0		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	**Adj. Relative Risk (95% C.I.)**	**p-Value**	**Covariate Remarks[a]**
All	***1.44 (0.89,2.32)***	***0.139***	AGE*BFAT (p=0.048) OCC*BFAT (p=0.002)
Officer	1.73 (0.82,3.64)	0.149	
Enlisted Flyer	0.61 (0.11,3.36)	0.574	
Enlisted Groundcrew	1.42 (0.72,2.79)	0.310	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 20-3. (Continued)
Analysis of Asthma

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Yes	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	171	4.7	1.17 (0.84,1.62)	0.357
Medium	172	1.7		
High	171	5.3		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)[c]			
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
514	1.11 (0.77,1.62)	0.573	AGE*PACKYR (p=0.027) RACE*BFAT (p=0.010)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 20-3. (Continued)
Analysis of Asthma

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Yes	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,056	2.7		
Background RH	370	4.3	1.59 (0.85,2.97)	0.150
Low RH	257	3.9	1.46 (0.70,3.04)	0.314
High RH	257	3.9	1.43 (0.69,3.00)	0.336
Low plus High RH	514	3.9	1.45 (0.81,2.59)	0.215

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	1,054			AGE*RACE (p=0.025) RACE*PACKYR (p=0.017) RACE*BFAT (p=0.014) OCC*BFAT (p=0.011)
Background RH	369	1.48 (0.77,2.84)	0.237	
Low RH	257	1.29 (0.58,2.85)	0.534	
High RH	257	1.28 (0.58,2.82)	0.547	
Low plus High RH	514	1.28 (0.69,2.38)	0.431	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 20-3. (Continued)
Analysis of Asthma

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Yes/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	3.4 (292)	4.7 (296)	4.1 (296)	1.05 (0.84,1.32)	0.653
5	4.7 (297)	3.1 (293)	4.4 (294)	1.00 (0.82,1.21)	0.973
6[c]	4.7 (296)	3.1 (293)	4.4 (294)	1.06 (0.85,1.30)	0.619

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	884	1.06 (0.80,1.42)**	0.674**	CURR*AGE (p=0.049) AGE*RACE (p=0.010) RACE*BFAT (p=0.007) OCC*BFAT (p=0.036)
5	884	0.99 (0.78,1.27)	0.962	AGE*RACE (p=0.010) RACE*BFAT (p=0.006) OCC (p=0.037)
6[d]	883	1.01 (0.80,1.27)**	0.965**	CURR*AGE (p=0.037) AGE*RACE (p=0.008) RACE*BFAT (p=0.004)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

** Log_2 (current dioxin + 1)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of the interaction; refer to Appendix Table P-2-1 for further analysis of this interaction.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.
CURR = Log_2 (current dioxin + 1).

Bronchitis

Differences between Ranch Hands and Comparisons were marginally significant in the Model 1 unadjusted and adjusted analyses of post-SEA bronchitis (Table 20-4(a,b): $p=0.098$, Est. $RR=1.21$; and $p=0.092$, Adj. $RR=1.21$ respectively). The percentage of Ranch Hands with a history of bronchitis (19.4%) was greater than the corresponding percentage of Comparisons (16.6%). When group differences were examined within occupation categories, enlisted flyers exhibited significant results in both the unadjusted and adjusted analyses (Table 20-4(a,b): $p=0.037$, Est. $RR=1.78$; and $p=0.033$, Adj. $RR=1.75$ respectively). A significantly higher percentage of Ranch Hand enlisted flyers had a history of bronchitis (26.9%) than the Comparison enlisted flyers (17.2%). No significant differences were found within the officer and enlisted groundcrew categories (Table 20-4(a,b): $p>0.23$ for all remaining contrasts). The covariates and interactions in the adjusted final model were industrial chemicals exposure, an occupation-by-body fat interaction, and an age-by-lifetime cigarette smoking history interaction.

None of the unadjusted analyses for Models 2 and 3 exhibited a significant association between post-SEA bronchitis and initial dioxin (Table 20-4(c,e): $p>0.11$ for all analyses). No significant covariates were retained in the Model 2 final adjusted model. In the Model 3 adjusted analyses, a significantly higher percentage of background Ranch Hands had a history of bronchitis (21.4%) than Comparisons (17.5%) (Table 20-4(f): $p=0.036$, Adj. $RR=1.40$). When occupation and body fat were removed from the final model, the results became marginally significant (Appendix Table P-3-2: $p=0.065$, Adj. $RR=1.33$). All other Model 3 adjusted contrasts were nonsignificant (Table 20-4(f): $p>0.84$ for all remaining contrasts). Significant covariates for Model 3 included lifetime cigarette smoking history, industrial chemicals exposure, and the interaction of occupation-by-body fat.

The unadjusted analyses for Models 4 and 5 uncovered no significant relationship between post-SEA bronchitis and current dioxin (Table 20-4(g): $p>0.14$ for both analyses). The unadjusted analysis of Model 6 displayed a marginally significant inverse association between current dioxin and post-SEA bronchitis (Table 20-4(g): $p=0.089$). The adjusted analysis of each model displayed a significant current dioxin-by-industrial chemical exposure interaction. Stratified results for each level of the interaction are presented in Appendix Table P-2-2. The final adjusted models, presented after deletion of the interaction, each indicate a significant inverse association between bronchitis and current dioxin (Table 20-4(h): $p\leq0.031$, Adj. $RR\leq0.89$ for all analyses). Occupation was a significant covariate in Models 4, 5, and 6, and lifetime cigarette smoking history also was included in Models 4 and 5. When occupation was removed from the final models, the results for Model 4 became marginally significant (Appendix Table P-3-2: $p=0.076$, Adj. $RR=0.90$), and the results for Model 5 became nonsignificant ($p=0.138$).

Pneumonia

In the unadjusted analysis of Model 1, the percentage of Ranch Hands with a history of pneumonia (8.5%) was significantly lower than the corresponding percentage of Comparisons (12.0%) (Table 20-5(a): $p=0.012$, Est. $RR=0.68$). Group contrasts evaluated within each occupation category exhibited similar results for the officer category (Table 20-5(a): Ranch

Table 20-4.
Analysis of Bronchitis

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	Group	n	Percent Yes	Est. Relative Risk (95% C.I.)	p-Value
All	*Ranch Hand*	*926*	*19.4*	*1.21 (0.97,1.51)*	*0.098*
	Comparison	*1,253*	*16.6*		
Officer	Ranch Hand	354	15.8	1.00 (0.68,1.45)	0.999
	Comparison	491	15.9		
Enlisted Flyer	Ranch Hand	156	26.9	1.78 (1.07,2.96)	0.037
	Comparison	198	17.2		
Enlisted Groundcrew	Ranch Hand	416	19.7	1.20 (0.86,1.66)	0.319
	Comparison	564	17.0		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks[a]
All	*1.21 (0.97,1.51)*	*0.092*	IC (p=0.066) OCC*BFAT (p=0.006) AGE*PACKYR (p=0.031)
Officer	0.99 (0.68,1.44)	0.943	
Enlisted Flyer	1.75 (1.05,2.93)	0.033	
Enlisted Groundcrew	1.22 (0.88,1.70)	0.237	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 20-4. (Continued)
Analysis of Bronchitis

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Yes	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	165	17.6	1.00 (0.84,1.19)	0.979
Medium	172	18.6		
High	168	17.3		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)[a]			
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
505	1.00 (0.84,1.19)	0.979	

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 20-4. (Continued)
Analysis of Bronchitis

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Yes	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,040	17.5		
Background RH	364	21.4	1.27 (0.94,1.72)	0.116
Low RH	251	17.9	1.04 (0.72,1.49)	0.847
High RH	254	17.7	1.02 (0.71,1.47)	0.902
Low plus High RH	505	17.8	1.03 (0.78,1.36)	0.838

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	1,038			PACKYR (p=0.027) IC (p=0.050) OCC*BFAT (p=0.002)
Background RH	363	1.40 (1.02,1.91)	0.036	
Low RH	251	0.98 (0.68,1.41)	0.917	
High RH	254	0.96 (0.66,1.40)	0.841	
Low plus High RH	505	0.97 (0.73,1.29)	0.844	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 20-4. (Continued)
Analysis of Bronchitis

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Yes/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	20.9 (287)	18.7 (289)	18.4 (293)	0.92 (0.81,1.03)	0.143
5	22.2 (293)	17.9 (285)	17.9 (291)	0.94 (0.85,1.04)	0.238
6[c]	21.9 (292)	17.9 (285)	17.9 (291)	0.91 (0.82,1.01)	0.089

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	868	0.84 (0.74,0.96)**	0.011**	CURR*IC (p=0.029) OCC (p=0.022) PACKYR (p=0.119)
5	868	0.89 (0.79,0.99)**	0.031**	CURR*IC (p=0.020) OCC (p=0.036) PACKYR (p=0.107)
6[d]	868	0.84 (0.74,0.94)**	0.004**	CURR*IC (p=0.020) OCC (p=0.014)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

** Log_2 (current dioxin + 1)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from model after deletion of this interaction; refer to Appendix Table P-2-2 for further analysis of this interaction.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 20-5.
Analysis of Pneumonia

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Percent Yes**	**Est. Relative Risk (95% C.I.)**	**p-Value**
All	***Ranch Hand***	***903***	***8.5***	***0.68 (0.51,0.92)***	***0.012***
	Comparison	***1,226***	***12.0***		
Officer	Ranch Hand	346	8.4	0.59 (0.37,0.93)	0.029
	Comparison	473	13.5		
Enlisted Flyer	Ranch Hand	151	11.3	1.00 (0.51,1.95)	0.999
	Comparison	195	11.3		
Enlisted Groundcrew	Ranch Hand	406	7.6	0.67 (0.43,1.06)	0.108
	Comparison	558	10.9		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	**Adj. Relative Risk (95% C.I.)**	**p-Value**	**Covariate Remarks[a]**
All	***0.68 (0.51,0.91)***	***0.008***	RACE (p=0.070) BFAT (p=0.071) AGE*PACKYR (p=0.032)
Officer	0.57 (0.36,0.90)	0.017	
Enlisted Flyer	0.99 (0.50,1.94)	0.965	
Enlisted Groundcrew	0.68 (0.43,1.07)	0.096	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 20-5. (Continued)
Analysis of Pneumonia

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Yes	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	160	9.4	0.87 (0.67,1.14)	0.309
Medium	168	6.0		
High	167	7.2		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)[a]			
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
495	0.87 (0.67,1.14)	0.309	

[a] Adjusted for percent body fat at the time of duty in SEA, and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 20-5. (Continued)
Analysis of Pneumonia

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Yes	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,020	12.5		
Background RH	350	10.6	0.85 (0.58,1.26)	0.424
Low RH	243	8.2	0.62 (0.38,1.01)	0.055
High RH	252	6.7	0.49 (0.29,0.83)	0.008
Low plus High RH	495	7.5	0.55 (0.37,0.81)	0.002

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	1,018			BFAT (p=0.098) AGE*PACKYR (p=0.029)
Background RH	349	0.85 (0.57,1.26)	0.421	
Low RH	243	0.59 (0.36,0.97)	0.038	
High RH	252	0.50 (0.29,0.86)	0.012	
Low plus High RH	495	0.55 (0.37,0.81)	0.002	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA, and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 20-5. (Continued)
Analysis of Pneumonia

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Yes/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	10.3 (273)	10.2 (283)	5.9 (289)	0.87 (0.73,1.03)	0.104
5	11.9 (278)	8.2 (281)	6.3 (286)	0.90 (0.78,1.04)	0.145
6[c]	11.9 (277)	8.2 (281)	6.3 (286)	0.89 (0.77,1.04)	0.156

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	844	0.86 (0.72,1.03)	0.095	AGE*PACKYR (p=0.009)
5	844	0.89 (0.77,1.03)	0.127	AGE*PACKYR (p=0.009)
6[d]	843	0.90 (0.76,1.05)	0.173	AGE*PACKYR (p=0.008)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Hands: 8.4%, Comparisons: 13.5%, p=0.029, Est. RR=0.59). Adjusted results also indicated a significant overall and officer group difference (Table 20-5(b): p=0.008, Adj. RR=0.68 and p=0.017, Adj. RR=0.57 respectively), and a marginally significant difference was found between Ranch Hands and Comparisons within the enlisted groundcrew stratum (Table 20-5(b): p=0.096, Adj. RR=0.68). In each of these analyses, more Comparisons had a history of post-SEA pneumonia than did Ranch Hands. An age-by-lifetime cigarette smoking history interaction, race, and body fat were retained in the final model.

The results of the Model 2 unadjusted analysis of post-SEA pneumonia were nonsignificant (Table 20-5(c): p=0.309, Est. RR=0.87). No covariates were significant in the adjusted model; thus, the unadjusted and adjusted results are identical. However, the Model 3 initial dioxin unadjusted and adjusted analyses detected several significant relationships. The contrast between Comparisons and Ranch Hands in the low initial dioxin category was marginally significant for the unadjusted analysis and significant for the adjusted analysis (Table 20-5(e,f): p=0.055, Est. RR=0.62 and p=0.038, Adj. RR=0.59 respectively). Fewer Ranch Hands in the low initial dioxin category had a history of pneumonia (8.2%) than the Comparisons (12.5%). The contrasts involving participants in the high Ranch Hand and low plus high Ranch Hand categories similarly demonstrated a significantly lower percentage of Ranch Hands with a history of post-SEA pneumonia than Comparisons (Table 20-5(e,f): p≤0.012 and Est. RR ≤0.55 for each contrast). Body fat and an age-by-lifetime cigarette smoking history interaction were retained in the Model 3 adjusted analysis.

For the unadjusted and adjusted analyses of post-SEA pneumonia for Models 4, 5, and 6, the adjusted analysis of Model 4 revealed a marginally significant negative association between history of pneumonia and current dioxin (Table 20-5(h): p=0.095, Adj. RR=0.86). All other analyses exhibited nonsignificant relationships between current dioxin and the occurrence of pneumonia (Table 20-5(g,h): p>0.10 for all analyses). The interaction of age-by-lifetime cigarette smoking history was significant in the final adjusted Models 4, 5, and 6.

Physical Examination Variable

Thorax and Lung Abnormalities

In the unadjusted and adjusted analyses of Model 1, significant differences between Ranch Hands and Comparisons in the occurrence of thorax and lung abnormalities were found overall and for the enlisted flyers specifically (Table 20-6(a): p=0.011, Est. RR=1.40 and p=0.012, Est. RR=2.11 respectively; Table 20-6(b): p=0.033, Est. RR=1.36 and p=0.021, Est. RR=2.07). For the overall category, the percentages of thorax and lung abnormalities were higher for Ranch Hands (14.2%) than for Comparisons (10.5%). Similarly, for enlisted flyers, the percentages were 22.8 for Ranch Hands and 12.3 for Comparisons. Significant covariates in the adjusted analysis of thorax and lung abnormalities included an age-by-lifetime cigarette smoking history interaction, occupation, and current cigarette smoking.

Model 2 unadjusted and adjusted analyses found no significant relationship between initial dioxin and thorax and lung abnormalities (Table 20-6(c,d): p>0.28 for all analyses).

Table 20-6.
Analysis of Thorax and Lung Abnormalities

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Percent Yes**	**Est. Relative Risk (95% C.I.)**	**p-Value**
All	***Ranch Hand***	***952***	***14.2***	***1.40 (1.09,1.81)***	***0.011***
	Comparison	***1,281***	***10.5***		
Officer	Ranch Hand	367	10.1	1.41 (0.88,2.27)	0.197
	Comparison	502	7.4		
Enlisted Flyer	Ranch Hand	162	22.8	2.11 (1.21,3.68)	0.012
	Comparison	203	12.3		
Enlisted Groundcrew	Ranch Hand	423	14.4	1.16 (0.81,1.67)	0.480
	Comparison	576	12.7		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	**Adj. Relative Risk (95% C.I.)**	**p-Value**	**Covariate Remarks[a]**
All	***1.36 (1.03,1.81)***	***0.033***	OCC (p<0.001) CSMOK (p<0.001) AGE*PACKYR (p=0.027)
Officer	1.40 (0.83,2.36)	0.206	
Enlisted Flyer	2.07 (1.12,3.82)	0.021	
Enlisted Groundcrew	1.11 (0.74,1.67)	0.602	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 20-6. (Continued)
Analysis of Thorax and Lung Abnormalities

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Yes	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	174	10.3	1.11 (0.92,1.35)	0.284
Medium	173	15.6		
High	173	12.7		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)[c]			
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
520	1.11 (0.87,1.42)	0.399	AGE ($p<0.001$) OCC ($p=0.027$) CSMOK ($p<0.001$) PACKYR ($p=0.109$)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 20-6. (Continued)
Analysis of Thorax and Lung Abnormalities

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Yes	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,063	10.4		
Background RH	374	15.2	1.48 (1.04,2.09)	0.028
Low RH	260	11.9	1.14 (0.74,1.75)	0.547
High RH	260	13.8	1.44 (0.96,2.17)	0.078
Low plus High RH	520	12.9	1.29 (0.93,1.78)	0.133

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	1,061			AGE ($p<0.001$) OCC ($p=0.001$) CSMOK ($p<0.001$) PACKYR ($p=0.003$)
Background RH	373	1.68 (1.12,2.50)	0.011	
Low RH	260	1.10 (0.69,1.75)	0.683	
High RH	260	1.26 (0.80,1.99)	0.316	
Low plus High RH	520	1.18 (0.82,1.69)	0.368	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 20-6. (Continued)
Analysis of Thorax and Lung Abnormalities

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Yes/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	16.3 (295)	11.3 (300)	14.1 (299)	0.94 (0.82,1.07)	0.334
5	15.3 (300)	12.5 (297)	13.8 (297)	0.95 (0.85,1.07)	0.408
6[c]	15.1 (299)	12.5 (297)	13.8 (297)	0.94 (0.84,1.06)	0.339

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	893	0.93 (0.79,1.09)**	0.369**	CURR*CSMOK (p=0.039) AGE (p<0.001) PACKYR (p=0.108) OCC*CSMOK (p=0.010)
5	893	0.95 (0.83,1.08)	0.446	AGE (p<0.001) PACKYR (p=0.057) OCC*CSMOK (p=0.042)
6[d]	892	0.97 (0.83,1.12)	0.665	AGE (p<0.001) PACKYR (p=0.054) OCC*CSMOK (p=0.039)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for $\log_2$ total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for $\log_2$ total lipids.

[d] Adjusted for $\log_2$ total lipids in addition to covariates specified under "Covariate Remarks" column.

** Log_2 (current dioxin +1)-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model after deletion of this interaction; refer to Appendix Table P-2-3 for further analysis of this interaction.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Significant differences between background Ranch Hands and Comparisons in the occurrence of thorax and lung abnormalities were uncovered in the Model 3 unadjusted and adjusted analysis (Table 20-6(e,f): p=0.028, Est. RR=1.48 and p=0.011, Adj. RR=1.68 respectively). The background Ranch Hands exhibited a higher percentage of thorax and lung abnormalities (15.2%) than Comparisons (10.4%). The unadjusted analysis also revealed a marginally significant difference between participants in the high Ranch Hand category, and Comparisons (Table 20-6(e): p=0.078, Est. RR=1.44). Both Models 2 and 3 were adjusted for age, occupation, current cigarette smoking, and lifetime cigarette smoking history.

When occupation was removed from the final adjusted analysis for Model 2, the results became marginally significant (Appendix Table P-3-4: p=0.087, Adj. RR=1.22). The significant result found in the Model 3 adjusted analysis of background Ranch Hands versus Comparisons became marginally significant (p=0.059). Also, the contrast of Ranch Hands in the high dioxin category versus Comparisons was marginally significant (p=0.068, Adj. RR=1.52) when occupation was removed from Model 3.

The association between current dioxin and thorax and lung abnormalities was nonsignificant in the analyses of Models 4, 5, and 6 (Table 20-6(g,h): p>0.33 for all analyses). Each of the three final adjusted models included age, lifetime cigarette smoking history, and an occupation-by-current cigarette smoking interaction. Model 4 also had a significant current dioxin-by-current cigarette smoking interaction (p=0.039). Results stratified by each level of the interaction are presented in Appendix Table P-2-3. Adjusted results in Table 20-6 for Model 4 were derived from the final model after deletion of the current dioxin-by-current cigarette smoking interaction.

Laboratory Examination Variables

X Ray Interpretation

Results from the Model 1 analysis of x ray interpretation exhibited no significant differences between Ranch Hands and Comparisons for the overall analysis or within any of the occupation strata (Table 20-7(a,b): p>0.27 for all contrasts). Age, occupation, and a lifetime cigarette smoking history-by-body fat interaction were retained in the final model.

No significant relationship between initial dioxin and x ray interpretation was detected in the analyses of Models 2 and 3 (Table 20-7(c-f): p>0.16 for all analyses). Model 2 was adjusted for age, occupation, and current cigarette smoking. Model 3 exhibited a significant categorized dioxin-by-occupation interaction (p=0.011). Results stratified by each level of occupation are presented in Appendix Table P-2-4. Model 3 was also adjusted for age and body fat.

Similar to Models 1 through 3, all unadjusted results for Models 4 through 6 for x ray interpretation were nonsignificant (Table 20-7(g): p>0.19 for all models). When adjusted for significant covariates, the final models for 4, 5, and 6 each included a current dioxin-by-current cigarette smoking interaction (Table 20-7(h): p=0.009, p=0.031, p=0.021 respectively). Stratified results for each model are presented in Appendix Table P-2-4.

Table 20-7.
Analysis of X Ray Interpretation

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	Group	n	Percent Abnormal	Est. Relative Risk (95% C.I.)	p-Value
All	***Ranch Hand***	***951***	***13.5***	***1.00 (0.78,1.28)***	***0.999***
	Comparison	***1,281***	***13.4***		
Officer	Ranch Hand	367	12.3	0.97 (0.65,1.47)	0.982
	Comparison	502	12.6		
Enlisted Flyer	Ranch Hand	162	19.1	1.42 (0.82,2.47)	0.271
	Comparison	203	14.3		
Enlisted Groundcrew	Ranch Hand	422	12.3	0.87 (0.60,1.27)	0.531
	Comparison	576	13.9		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks[a]
All	***0.98 (0.76,1.25)***	***0.861***	AGE (p<0.001) OCC (p=0.018) PACKYR*BFAT (p=0.030)
Officer	0.96 (0.64,1.45)	0.846	
Enlisted Flyer	1.34 (0.77,2.35)	0.302	
Enlisted Groundcrew	0.86 (0.59,1.25)	0.432	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 20-7. (Continued)
Analysis of X Ray Interpretation

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Abnormal	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	174	10.9	0.93 (0.76,1.14)	0.490
Medium	173	16.8		
High	172	9.9		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)[c]			
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
519	0.85 (0.67,1.07)	0.162	AGE (p=0.028) OCC (p=0.001) CSMOK (p=0.052)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 20-7. (Continued)
Analysis of X Ray Interpretation

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,063	13.7		
Background RH	374	14.4	1.06 (0.75,1.48)	0.756
Low RH	260	13.5	0.98 (0.66,1.45)	0.901
High RH	259	11.6	0.83 (0.54,1.26)	0.376
Low plus High RH	519	12.5	0.90 (0.66,1.23)	0.515

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	1,063			DXCAT*OCC (p=0.011) AGE (p<0.001) BFAT (p=0.111)
Background RH	374	1.12 (0.79,1.59)**	0.530**	
Low RH	260	0.92 (0.62,1.38)**	0.690**	
High RH	259	0.79 (0.51,1.21)**	0.279**	
Low plus High RH	519	0.86 (0.62,1.18)**	0.343**	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

** Categorized dioxin-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model after deletion of this interaction; refer to Appendix Table P-2-4 for further analysis of this interaction.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.
DXCAT = Categorized Dioxin.

Table 20-7. (Continued)
Analysis of X Ray Interpretation

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Abnormal/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	12.9 (295)	14.0 (300)	13.1 (298)	0.94 (0.82,1.07)	0.339
5	14.0 (300)	12.8 (297)	13.2 (296)	0.97 (0.87,1.09)	0.651
6[c]	14.0 (299)	12.8 (297)	13.2 (296)	0.92 (0.82,1.04)	0.197

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	892	****	****	CURR*CSMOK (p=0.009) AGE (p=0.006) OCC (p=0.035) PACKYR (p=0.108)
5	892	0.95 (0.84,1.09)**	0.478**	CURR*CSMOK (p=0.031) AGE (p=0.005) OCC (p=0.054) PACKYR (p=0.104)
6[d]	892	0.88 (0.77,1.02)**	0.085**	CURR*CSMOK (p=0.021) AGE (p=0.002) OCC (p=0.016)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

** Log_2 (current dioxin + 1)-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model after deletion of this interaction; refer to Appendix Table P-2-4 for further analysis of this interaction.

**** Log_2 (current dioxin + 1)-by-covariate interaction ($p\leq0.01$); adjusted relative risk, confidence interval, and p-value not presented; refer to Appendix Table P-2-4 for further analysis of this interaction.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 20-7(h) displays adjusted results from Models 5 and 6 after deletion of the current dioxin-by-current cigarette smoking interactions. For Model 4, the stratified analyses did not exhibit a significant association between current dioxin and an abnormal x ray interpretation except for Ranch Hands who smoked more than 20 cigarettes a day ($p=0.002$, Adj. RR=0.48). For this category, the percentage of abnormal x ray interpretations decreased as the level of current dioxin increased (low = 34.6%, medium = 10.7%, high = 2.8%). Model 6 displayed a marginally significant negative association between current dioxin and x ray interpretation after deletion of the interaction between current dioxin and current cigarette smoking (Table 20-7(h): $p=0.085$, Est. RR=0.88). Models 4 and 5 also were adjusted for age, occupation, and lifetime cigarette smoking history, and Model 6 also included age and occupation. When occupation was removed from Model 6, the results became nonsignificant (Appendix Table P-3-5: $p=0.491$).

FVC

The unadjusted and adjusted Model 1 analyses of FVC revealed no significant differences in group means across or within occupational categories (Table 20-8(a,b): $p>0.25$ for all analyses). The adjusted analysis contained occupation, current cigarette smoking, body fat, an age-by-lifetime cigarette smoking history interaction, and a race-by-lifetime cigarette smoking history interaction.

The unadjusted analysis of Model 2 did not detect a significant association between initial dioxin and FVC (Table 20-8(c): $p=0.305$). However, the Model 2 adjusted analysis revealed a significant negative association between initial dioxin and FVC (Table 20-8(d): $p=0.034$). The means decreased from 94.8 percent of predicted for the low initial dioxin category to 94.3 and 91.5 percent for the medium and high initial dioxin categories. Age, race, body fat, an occupation-by-industrial chemical exposure interaction, and a lifetime cigarette smoking history-by-industrial chemicals exposure interaction were significant in Model 2.

For the unadjusted Model 3 analysis, the contrast of Comparisons versus Ranch Hands in the low plus high dioxin category was marginally significant (Table 20-8(e): $p=0.089$). The Ranch Hands in the low plus high dioxin category had a lower mean FVC (99.2 percent) than the Comparisons (100.5 percent). All Model 3 adjusted contrasts were nonsignificant (Table 20-8(f): $p>0.18$). Current cigarette smoking, body fat, an age-by-lifetime cigarette smoking history interaction, a race-by-lifetime cigarette smoking history interaction, and an occupation-by-industrial chemicals exposure interaction were significant in Model 3. When occupation and body fat were removed from the final model, Ranch Hands in the high dioxin category had marginally significant mean lower FVC values than Comparisons (Appendix Table P-3-6: high Ranch Hands: Adj. mean=93.8 percent; Comparisons: Adj. mean=95.4 percent; $p=0.089$). For FVC, lower values indicate greater compromise in lung function.

The unadjusted analysis of FVC versus current dioxin demonstrated significant negative associations (Table 20-8(g): $p\leq0.015$ for Models 4, 5, and 6). However, when each model was adjusted for covariate effects, all associations were nonsignificant (Table 20-8(h): $p>0.22$ for all analyses). Models 4, 5, and 6 were adjusted for age, body fat, and the interactions of lifetime cigarette smoking history-by-race, current cigarette smoking-by-

Table 20-8.
Analysis of FVC (Percent of Predicted)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	Group	n	Mean	Difference of Means (95% C.I.)	p-Value
All	***Ranch Hand***	***951***	***100.1***	***-0.3 (-1.5,0.9)***	***0.607***
	Comparison	***1,280***	***100.5***		
Officer	Ranch Hand	366	101.6	-0.8 (-2.7,1.2)	0.439
	Comparison	502	102.4		
Enlisted Flyer	Ranch Hand	162	99.8	1.3 (-1.7,4.3)	0.393
	Comparison	203	98.5		
Enlisted Groundcrew	Ranch Hand	423	99.0	-0.5 (-2.3,1.3)	0.597
	Comparison	575	99.5		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	Group	n	Adj. Mean	Difference of Adj. Means (95% C.I.)	p-Value	Covariate Remarks[a]
All	***Ranch Hand***	***950***	***95.3***	***-0.2 (-1.4,0.9)***	***0.665***	OCC (p=0.027)
	Comparison	***1,278***	***95.6***			CSMOK (p<0.001)
						BFAT (p<0.001)
Officer	Ranch Hand	365	96.4	-0.4 (-2.2,1.4)	0.677	AGE*PACKYR (p=0.012)
	Comparison	502	96.8			PACKYR*RACE (p=0.001)
Enlisted Flyer	Ranch Hand	162	96.0	1.6 (-1.2,4.4)	0.255	
	Comparison	203	94.4			
Enlisted Groundcrew	Ranch Hand	423	94.3	-0.8 (-2.5,0.9)	0.341	
	Comparison	573	95.1			

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 20-8. (Continued)
Analysis of FVC (Percent of Predicted)

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED						
Initial Dioxin Category Summary Statistics				Analysis Results for Log_2 (Initial Dioxin)[a]		
Initial Dioxin	n	Mean	Adj. Mean[a]	R^2	Slope (Std. Error)	p-Value
Low	174	99.1	98.8	0.040	-0.471 (0.458)	0.305
Medium	173	99.8	99.7			
High	173	97.2	97.6			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[b]			
Initial Dioxin	n	Adj. Mean[b]	R^2	Adj. Slope (Std. Error)[b]	p-Value	Covariate Remarks
Low	174	94.8	0.167	-1.068 (0.502)	0.034	AGE (p=0.001) RACE (p<0.001) BFAT (p=0.007) OCC*IC (p=0.003) PACKYR*IC (p=0.015)
Medium	173	94.3				
High	173	91.5				

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 20-8. (Continued)
Analysis of FVC (Percent of Predicted)

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED					
Dioxin Category	n	Mean	Adj. Mean[a]	Difference of Adj. Mean vs. Comparisons (95% C.I.)	p-Value
Comparison	1,062	100.5	100.5		
Background RH	373	102.0	101.2	0.7 (-1.0,2.3)	0.439
Low RH	260	99.0	99.2	-1.3 (-3.2,0.7)	0.196
High RH	260	98.3	99.2	-1.3 (-3.2,0.6)	0.179
Low plus High RH	520	98.7	99.2	-1.3 (-2.8,0.2)	0.089

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED					
Dioxin Category	n	Adj. Mean[b]	Difference of Adj. Mean vs. Comparisons (95% C.I.)	p-Value	Covariate Remarks
Comparison	1,060	95.7			CSMOK ($p<0.001$) BFAT ($p<0.001$) AGE*PACKYR ($p=0.007$) PACKYR*RACE ($p<0.001$) OCC*IC ($p=0.022$)
Background RH	372	96.1	0.3 (-1.3,1.9)	0.698	
Low RH	260	95.5	-0.3 (-2.1,1.5)	0.766	
High RH	260	94.5	-1.3 (-3.1,0.6)	0.183	
Low plus High RH	520	95.0	-0.8 (-2.2,0.7)	0.298	

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 20-8. (Continued)
Analysis of FVC (Percent of Predicted)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[a]	Low	Medium	High	R^2	Slope (Std. Error)	p-Value
4	102.2 (295)	99.5 (299)	98.4 (299)	0.011	-1.023 (0.323)	0.002
5	102.5 (300)	99.4 (296)	98.2 (297)	0.012	-0.919 (0.277)	0.001
6[b]	102.2 (299)	99.4 (296)	98.6 (297)	0.016	-0.728 (0.299)	0.015

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	Low	Medium	High	R^2	Adj. Slope (Std. Error)	p-Value	Covariate Remarks
4	95.9 (294)	95.2 (299)	94.6 (299)	0.179	-0.385 (0.360)	0.286	AGE (p<0.001) BFAT (p<0.001) PACKYR*RACE (p=0.026) CSMOK*OCC (p<0.001) OCC*IC (p=0.002) PACKYR*IC (p=0.034)
5	96.1 (299)	95.0 (296)	94.4 (297)	0.180	-0.367 (0.305)	0.228	AGE (p<0.001) BFAT (p<0.001) PACKYR*RACE (p=0.027) CSMOK*OCC (p=0.001) OCC*IC (p=0.002) PACKYR*IC (p=0.034)
6[c]	95.7 (298)	94.9 (296)	94.7 (297)	0.183	-0.172 (0.329)	0.600	AGE (p=0.001) BFAT (p<0.001) PACKYR*RACE (p=0.032) CSMOK*OCC (p=0.001) OCC*IC (p=0.002) PACKYR*IC (p=0.035)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Adjusted for log_2 total lipids.

[c] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

occupation, occupation-by-industrial chemicals exposure, and lifetime cigarette smoking history-by-industrial chemicals exposure. When occupation and body fat were removed from the final models of 4, 5, and 6, each association between current dioxin and FVC became highly significant (Appendix Table P-3-6: $p \leq 0.002$ for all models). Similar to the unadjusted analysis, the association between FVC and current dioxin was negative such that the mean FVC decreased for increasing levels of current dioxin, indicating a higher risk of lung dysfunction for higher levels of current dioxin.

FEV_1

No significant differences in means between Ranch Hands and Comparisons were revealed in the unadjusted or adjusted analysis of percent of predicted FEV_1 (Table 20-9(a,b): $p > 0.32$ for all analyses). Covariates retained in the final model were body fat, and the interactions of current cigarette smoking-by-occupation, age-by-lifetime cigarette smoking history, and race-by-lifetime cigarette smoking history.

The unadjusted Model 2 analysis and the unadjusted and adjusted Model 3 analyses did not detect any significant associations between initial dioxin and FEV_1 (Table 20-9(c,e,f): $p > 0.25$ for all analyses). The adjusted analysis for Model 2 exhibited a significant initial dioxin-by-current cigarette smoking interaction (Table 20-9(d): $p = 0.002$). Results stratified by each level of the interaction are displayed in Appendix Table P-2-5. The stratified analyses exhibited a significant negative association between initial dioxin and FEV_1 for Ranch Hands who never smoked ($p = 0.001$). The adjusted means for this stratum were 98.6, 96.4, and 90.8 percent for the low, medium, and high levels of initial dioxin respectively. The association was nonsignificant within the other current cigarette smoking strata (Appendix Table P-2-5: $p > 0.10$). The adjusted slopes of the individual smoking strata increased with a rise in the level of smoking. The final adjusted model for Model 2 also included the covariates age, race, lifetime cigarette smoking history, body fat and industrial chemicals exposure. Model 3 was adjusted for industrial chemicals exposure, and the interactions of age-by-lifetime cigarette smoking history, age-by-body fat, lifetime cigarette smoking history-by-race, current cigarette smoking-by-occupation, and body fat-by-occupation.

All analyses of Models 4, 5, and 6 resulted in nonsignificant associations between current dioxin and FEV_1 (Table 20-9(g,h): $p \geq 0.19$ for all analyses). Final adjusted models each included race, lifetime cigarette smoking history, an age-by-body fat interaction, and a current cigarette smoking-by-occupation interaction. Models 4 and 6 also included an occupation-by-industrial chemicals exposure interaction, while Model 5 also included industrial chemicals exposure.

Ratio of Observed FEV_1 to Observed FVC

Due to the distribution of the data, a natural logarithm (1-X) transformation was used. Because of this transformation, a negative slope (Models 2, 4, 5, and 6) implies a positive association between dioxin and the ratio of observed FEV_1 to observed FVC.

Table 20-9.
Analysis of FEV_1 (Percent of Predicted)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	Group	n	Mean	Difference of Means (95% C.I.)	p-Value
All	***Ranch Hand***	***951***	***94.6***	***-0.7 (-2.2,0.7)***	***0.329***
	Comparison	***1,280***	***95.3***		
Officer	Ranch Hand	366	95.7	-1.1 (-3.4,1.2)	0.352
	Comparison	502	96.8		
Enlisted Flyer	Ranch Hand	162	91.3	-0.9 (-4.4,2.7)	0.638
	Comparison	203	92.2		
Enlisted Groundcrew	Ranch Hand	423	94.8	-0.2 (-2.4,1.9)	0.826
	Comparison	575	95.1		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	Group	n	Adj. Mean	Difference of Adj. Means (95% C.I.)	p-Value	Covariate Remarks[a]
All	***Ranch Hand***	***950***	***91.1***	***-0.4 (-1.7,0.9)***	***0.531***	BFAT (p<0.001)
	Comparison	***1,278***	***94.5***			CSMOK*OCC (p=0.038)
Officer	Ranch Hand	365	92.6	-0.5 (-2.6,1.6)	0.659	AGE*PACKYR (p=0.002)
	Comparison	502	93.0			PACKYR*RACE (p=0.015)
Enlisted Flyer	Ranch Hand	162	90.5	-0.1 (-3.4,3.1)	0.938	
	Comparison	203	90.6			
Enlisted Groundcrew	Ranch Hand	423	90.3	-0.5 (-2.5,1.5)	0.633	
	Comparison	573	90.8			

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 20-9. (Continued)
Analysis of FEV_1 (Percent of Predicted)

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED						
Initial Dioxin Category Summary Statistics				Analysis Results for Log_2 (Initial Dioxin)[a]		
Initial Dioxin	n	Mean	Adj. Mean[a]	R^2	Slope (Std. Error)	p-Value
Low	174	93.9	93.9	0.006	0.125 (0.568)	0.826
Medium	173	93.7	93.7			
High	173	95.4	95.4			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[b]			
Initial Dioxin	n	Adj. Mean[b]	R^2	Adj. Slope (Std. Error)	p-Value	Covariate Remarks
Low	174	****	0.159	****	****	INIT*CSMOK (p=0.002) AGE (p<0.001) RACE (p<0.001) PACKYR (p<0.001) BFAT (p=0.019) IC (p=0.082)
Medium	173	****				
High	173	****				

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

**** Log_2 (initial dioxin)-by-covariate interaction ($p \leq 0.01$); adjusted mean, adjusted slope, standard error, and p-value not presented; refer to Appendix Table P-2-5 for further analysis of this interaction.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.
INIT = Log_2 (initial dioxin).

Table 20-9. (Continued)
Analysis of FEV_1 (Percent of Predicted)

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED					
Dioxin Category	n	Mean	Adj. Mean[a]	Difference of Adj. Mean vs. Comparisons (95% C.I.)	p-Value
Comparison	1,062	95.3	95.3		
Background RH	373	94.7	94.6	-0.7 (-2.8,1.3)	0.492
Low RH	260	93.9	93.9	-1.4 (-3.7,1.0)	0.257
High RH	260	94.7	94.9	-0.4 (-2.8,2.0)	0.743
Low plus High RH	520	94.3	94.4	-0.9 (-2.7,0.9)	0.345

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED					
Dioxin Category	n	Adj. Mean[b]	Difference of Adj. Mean vs. Comparisons (95% C.I.)	p-Value	Covariate Remarks
Comparison	1,060	91.5			IC (p=0.066) AGE*PACKYR (p=0.003) AGE*BFAT (p=0.001) PACKYR*RACE (p=0.009) CSMOK*OCC (p=0.009) BFAT*OCC (p=0.008)
Background RH	372	90.5	-1.0 (-2.9,0.9)	0.315	
Low RH	260	91.4	-0.1 (-2.2,2.1)	0.932	
High RH	260	90.9	-0.6 (-2.8,1.6)	0.583	
Low plus High RH	520	91.2	-0.3 (-2.0,1.3)	0.684	

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 20-9. (Continued)
Analysis of FEV_1 (Percent of Predicted)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[a]	Low	Medium	High	R^2	Slope (Std. Error)	p-Value
4	95.0 (295)	94.0 (299)	94.4 (299)	<0.001	0.231 (0.405)	0.568
5	95.3 (300)	93.7 (296)	94.5 (297)	<0.001	0.107 (0.347)	0.757
6[b]	94.7 (299)	93.6 (296)	95.2 (297)	0.008	0.437 (0.374)	0.243

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	Low	Medium	High	R^2	Adj. Slope (Std. Error)	p-Value	Covariate Remarks
4	89.3 (294)	90.0 (299)	90.1 (299)	0.190	0.447 (0.448)	0.318	RACE (p<0.001) PACKYR (p<0.001) AGE*BFAT (p=0.020) CSMOK*OCC (p=0.001) OCC*IC (p=0.050)
5	89.3 (299)	89.4 (296)	90.2 (297)	0.185	0.301 (0.379)	0.428	RACE (p<0.001) PACKYR (p<0.001) IC (p=0.082) AGE*BFAT (p=0.021) CSMOK*OCC (p=0.001)
6[c]	89.0 (298)	89.5 (296)	90.7 (297)	0.192	0.536 (0.409)	0.190	RACE (p<0.001) PACKYR (p<0.001) AGE*BFAT (p=0.023) CSMOK*OCC (p=0.001) OCC*IC (p=0.044)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Adjusted for log_2 total lipids.

[c] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

For the Model 1 unadjusted and adjusted analyses of the ratio of observed FEV_1 to observed FVC, all mean differences between Ranch Hands and Comparisons were nonsignificant (Table 20-10(a,b): $p>0.19$ for all contrasts). Lifetime cigarette smoking history, body fat, industrial chemical exposure, and the interactions of current cigarette smoking-by-race and age-by-occupation were included in the final model.

The Model 2 unadjusted analysis exhibited a significant inverse association between the ratio of observed FEV_1 to observed FVC and initial dioxin (Table 20-10(c): $p=0.008$). After Model 2 was adjusted for age, race, occupation, current cigarette smoking, lifetime cigarette smoking history, and industrial chemicals exposure, the association between the FEV_1 to FVC ratio and initial dioxin became nonsignificant (Table 20-10(d): $p=0.165$). Model 3 unadjusted analyses indicated significant differences in means between Comparisons and background Ranch Hands and between Comparisons and Ranch Hands in the high dioxin category (Table 20-10(e): $p=0.009$ and 0.022, Est. difference in means = -0.012 and 0.012). Adjusted contrasts revealed a marginally significant difference between Comparisons and background Ranch Hands (Table 20-10(f): $p=0.070$, Est. difference in means = -0.007). Covariates that displayed significance in Model 3 were a categorized dioxin-by-age interaction, lifetime cigarette smoking history, industrial chemicals exposure, and age-by-occupation, age-by-body fat, current cigarette smoking-by-race, and body fat-by-occupation interactions. Results in Table 20-10(f) are those from Model 3 after deletion of the categorized dioxin-by-age interaction from the final adjusted model. Stratified results for each level of age are displayed in Appendix Table P-2-6.

Analyses of Models 4 through 6 indicated significant positive associations between the ratio of observed FEV_1 to observed FVC and current dioxin (Table 20-10(g,h): $p\leq0.001$ for all analyses). For Model 4, the adjusted mean ratios were 0.767, 0.755, and 0.782 for the low, medium, and high current dioxin categories respectively; for Model 5, the adjusted mean ratios were 0.766, 0.774, 0.785, and for Model 6 the adjusted mean ratios were 0.765, 0.773, and 0.785. Due to the transformation used, the negative slope between 1 minus the FEV_1 to FVC ratio and current dioxin for each model indicates an increasing trend in the FEV_1 to FVC ratio as current dioxin increased. Each adjusted model included race, current cigarette smoking, lifetime cigarette smoking history, industrial chemicals exposure, and an age-by-body fat interaction.

Loss of Vital Capacity

The Model 1 unadjusted analysis of loss of vital capacity did not detect any overall group differences (Table 20-11(a): $p>0.26$). However, after stratifying by occupation, a marginally significant difference was detected between enlisted flyer Ranch Hands and Comparisons for the mild versus no loss of vital capacity contrast (Table 20-11(a): $p=0.089$, Est. RR=0.46). The percentage of enlisted flyer Ranch Hands with mild loss of vital capacity was lower than the percentage of Comparisons (4.3% vs. 8.9%). All other unadjusted contrasts, including those performed for moderate or severe loss versus no loss of vital capacity, were nonsignificant (Table 20-11(a): $p>0.37$ for all). Paralleling the unadjusted analysis, the adjusted analysis of mild loss versus no loss of vital capacity was also significant for the enlisted flyers (Table 20-11(b): $p=0.048$, Adj. RR=0.39). All other adjusted analyses were not significant ($p>0.24$). The Model 1 analysis was adjusted for

Table 20-10.
Analysis of Ratio of Observed FEV_1 to Observed FVC

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	Group	n	Mean[a]	Difference of Means (95% C.I.)[b]	p-Value[c]
All	***Ranch Hand***	***951***	***0.760***	***-0.002 --***	***0.569***
	Comparison	***1,280***	***0.762***		
Officer	Ranch Hand	366	0.752	-0.004 --	0.450
	Comparison	502	0.755		
Enlisted Flyer	Ranch Hand	162	0.741	-0.012 --	0.193
	Comparison	203	0.753		
Enlisted Groundcrew	Ranch Hand	423	0.774	0.003 --	0.496
	Comparison	575	0.771		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	Group	n	Adj. Mean[a]	Difference of Adj. Means (95% C.I.)[b]	p-Value[c]	Covariate Remarks[d]
All	***Ranch Hand***	***950***	***0.772***	***-0.001 --***	0.853	PACKYR (p<0.001) BFAT (p<0.001) IC (p=0.068) AGE*OCC (p<0.001) CSMOK*RACE (p=0.003)
	Comparison	***1,278***	***0.772***			
Officer	Ranch Hand	365	0.770	-0.002 --	0.633	
	Comparison	502	0.772			
Enlisted Flyer	Ranch Hand	162	0.768	-0.008 --	0.232	
	Comparison	203	0.776			
Enlisted Groundcrew	Ranch Hand	423	0.775	0.004 --	0.371	
	Comparison	573	0.772			

[a] Transformed from the natural logarithm (1-X) scale.

[b] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm (1-X) scale.

[c] P-values based on difference of means on natural logarithm (1-X) scale.

[d] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 20-10. (Continued)
Analysis of Ratio of Observed FEV_1 to Observed FVC

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED						
Initial Dioxin Category Summary Statistics				Analysis Results for Log_2 (Initial Dioxin)[b]		
Initial Dioxin	n	Mean[a]	Adj. Mean[ab]	R^2	Slope (Std. Error)[c]	p-Value
Low	174	0.761	0.762	0.052	-0.029 (0.011)	0.008
Medium	173	0.758	0.759			
High	173	0.791	0.789			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	174	0.781	0.201	-0.016 (0.012)	0.165	AGE ($p<0.001$) RACE ($p=0.004$)
Medium	173	0.780				OCC ($p=0.133$) CSMOK ($p=0.134$)
High	173	0.799				PACKYR ($p<0.001$) IC ($p=0.043$)

[a] Transformed from natural logarithm (1-X) scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Slope and standard error based on natural logarithm of (1 - ratio of observed FEV_1 to observed FVC) versus $\log_2$ (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 20-10. (Continued)
Analysis of Ratio of Observed FEV_1 to Observed FVC

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED					
Dioxin Category	n	Mean[a]	Adj. Mean[ab]	Difference of Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]
Comparison	1,062	0.762	0.762		
Background RH	373	0.746	0.750	-0.012 --	0.009
Low RH	260	0.763	0.762	0.000 --	0.990
High RH	260	0.778	0.774	0.012 --	0.022
Low plus High RH	520	0.770	0.768	0.006 --	0.136

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED					
Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	1,060	0.773**			DXCAT*AGE ($p=0.047$) PACKYR ($p<0.001$) IC ($p=0.007$) AGE*OCC ($p<0.001$) AGE*BFAT ($p=0.006$) CSMOK*RACE ($p=0.018$) BFAT*OCC ($p=0.016$)
Background RH	372	0.766**	-0.007 --**	0.070**	
Low RH	260	0.776**	0.003 --**	0.536**	
High RH	260	0.777**	0.004 --**	0.400**	
Low plus High RH	520	0.776**	0.003 --**	0.344**	

[a] Transformed from natural logarithm (1-X) scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Difference of adjusted means after transformation to original scale; confidence interval on difference of adjusted means not presented because analysis was performed on natural logarithm (1-X) scale.

[d] P-value is based on difference of means on natural logarithm (1-X) scale.

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

** Categorized dioxin-by-covariate interaction ($0.01<p\leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model after deletion of this interaction; refer to Appendix Table P-2-6 for further analysis of this interaction.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 20-10. (Continued)
Analysis of Ratio of Observed FEV_1 to Observed FVC

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[b]	Low	Medium	High	R^2	Slope (Std. Error)[c]	p-Value
4	0.746 (295)	0.758 (299)	0.776 (299)	0.041	-0.046 (0.007)	<0.001
5	0.746 (300)	0.757 (296)	0.778 (297)	0.035	-0.037 (0.006)	<0.001
6[d]	0.743 (299)	0.757 (296)	0.780 (297)	0.042	-0.043 (0.007)	<0.001

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[b]	Low	Medium	High	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
4	0.767 (294)	0.755 (299)	0.782 (299)	0.233	-0.025 (0.007)	0.001	RACE (p=0.002) CSMOK (p=0.001) PACKYR (p<0.001) IC (p=0.014) AGE*BFAT (p=0.006)
5	0.766 (299)	0.774 (296)	0.785 (297)	0.232	-0.020 (0.006)	0.001	RACE (p=0.001) CSMOK (p=0.001) PACKYR (p<0.001) IC (p=0.016) AGE*BFAT (p=0.007)
6[e]	0.765 (298)	0.773 (296)	0.785 (297)	0.232	-0.022 (0.007)	0.001	RACE (p=0.002) CSMOK (p=0.001) PACKYR (p<0.001) IC (p=0.015) AGE*BFAT (p=0.007)

[a] Transformed from natural logarithm (1-X) scale.

[b] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[c] Slope and standard error based on natural logarithm of (1 - ratio of observed FEV_1 to observed FVC) versus log_2 (current dioxin + 1).

[d] Adjusted for log_2 total lipids.

[e] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 20-11.
Analysis of Loss of Vital Capacity

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED

Occupational Category	Group	n	Percent: None	Percent: Mild	Percent: Mod. or Sev.	Mild vs. None: Est. Relative Risk (95% C.I.)	Mild vs. None: p-Value	Moderate or Severe vs. None: Est. Relative Risk (95% C.I.)	Moderate or Severe vs. None: p-Value
All	*Ranch Hand*	*951*	*93.5*	*5.4*	*1.1*	*0.81 (0.57,1.17)*	*0.263*	*0.78 (0.36,1.71)*	*0.535*
	Comparison	*1,280*	*92.2*	*6.5*	*1.3*				
Officer	Ranch Hand	366	94.6	4.6	0.8	0.86 (0.46,1.60)	0.628	1.02 (0.23,4.59)	0.978
	Comparison	502	93.8	5.4	0.8				
Enlisted Flyer	Ranch Hand	162	94.5	4.3	1.2	0.46 (0.19,1.13)	0.089	0.47 (0.09,2.46)	0.371
	Comparison	203	88.6	8.9	2.5				
Enlisted Groundcrew	Ranch Hand	423	92.4	6.4	1.2	0.96 (0.58,1.60)	0.880	0.85 (0.27,2.60)	0.770
	Comparison	575	92.0	6.6	1.4				

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED

Occupational Category	Mild vs. None: Adj. Relative Risk (95% C.I.)	Mild vs. None: p-Value	Moderate or Severe vs. None: Adj. Relative Risk (95% C.I.)	Moderate or Severe vs. None: p-Value	Covariate Remarks[a]
All	*0.80 (0.55,1.16)*	*0.248*	*0.78 (0.35,1.73)*	*0.538*	AGE (p<0.001) CSMOK (p=0.003) BFAT (p<0.001) IC (p=0.114) RACE*PACKYR (p=0.011)
Officer	0.80 (0.42,1.53)	0.503	1.01 (0.22,4.60)	0.989	
Enlisted Flyer	0.39 (0.16,0.99)	0.048	0.37 (0.07,1.99)	0.244	
Enlisted Groundcrew	1.05 (0.62,1.78)	0.861	0.95 (0.30,3.02)	0.930	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 20-11. (Continued)
Analysis of Loss of Vital Capacity

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED								
Initial Dioxin Category Summary Statistics					Analysis Results for Log_2 (Initial Dioxin)[a]			
		Percent			Mild vs. None		Moderate or Severe vs. None	
Initial Dioxin Category	n	None	Mild	Mod. or Sev.	Est. Relative Risk (95% C.I.)[b]	p-Value	Est. Relative Risk (95% C.I.)[b]	p-Value
Low	174	92.0	6.3	1.7	1.05 (0.80,1.37)	0.720	0.80 (0.45,1.43)	0.452
Medium	173	94.2	4.1	1.7				
High	173	92.5	6.4	1.2				

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED					
Analysis Results for Log_2 (Initial Dioxin)[c]					
	Mild vs. None		Moderate or Severe vs. None		
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
520	1.16 (0.85,1.59)	0.353	0.80 (0.36,1.77)	0.574	AGE (p=0.013) BFAT (p=0.056) RACE*PACKYR (p=0.010) OCC*IC (p=0.022)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 20-11. (Continued)
Analysis of Loss of Vital Capacity

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED								
		Percent			Mild vs. None		Moderate or Severe vs. None	
Dioxin Category	n	None	Mild	Mod. or Sev.	Est. Relative Risk (95% C.I.)[ab]	p-Value	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,062	92.0	6.5	1.5				
Background RH	373	94.1	5.4	0.5	0.94 (0.56,1.57)	0.802	0.41 (0.09,1.79)	0.233
Low RH	260	92.7	5.4	1.9	0.77 (0.43,1.40)	0.397	1.19 (0.43,3.30)	0.738
High RH	260	93.1	5.8	1.2	0.77 (0.43,1.38)	0.384	0.65 (0.19,2.28)	0.504
Low plus High RH	520	92.9	5.6	1.5	0.77 (0.49,1.21)	0.263	0.91 (0.38,2.16)	0.833

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED						
		Mild vs. None		Moderate or Severe vs. None		
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	1,060					AGE ($p<0.001$) CSMOK ($p=0.006$) BFAT ($p=0.007$) IC ($p=0.145$) RACE*PACKYR ($p=0.004$)
Background RH	372	0.94 (0.55,1.62)	0.833	0.43 (0.10,1.95)	0.277	
Low RH	260	0.67 (0.36,1.23)	0.196	0.97 (0.34,2.77)	0.952	
High RH	260	0.84 (0.46,1.54)	0.582	0.74 (0.20,2.67)	0.643	
Low plus High RH	520	0.75 (0.47,1.19)	0.220	0.87 (0.36,2.11)	0.754	

[a] Relative risk and confidence interval relative to Comparisons.
[b] Adjusted for percent body fat at the time of duty in SEA and change in body fat from the time of duty in SEA to the date of the blood draw for dioxin.
[c] Adjusted for percent body fat at the time of duty in SEA, change in body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin ≤ 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin ≤ 10 ppt, Initial Dioxin > 143 ppt.

Table 20-11. (Continued)
Analysis of Loss of Vital Capacity

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED									
	Current Dioxin Category Summary Statistics					Analysis Results for Log_2 (Current Dioxin + 1)			
			Percent			Mild vs. None		Moderate or Severe vs. None	
Model[a]	Current Dioxin Category	n	None	Mild	Mod. or Sev.	Est. Relative Risk (95% C.I.)[b]	p-Value	Est. Relative Risk (95% C.I.)[b]	p-Value
4	Low	295	94.6	4.7	0.7	1.12 (0.93,1.36)	0.231	1.09 (0.72,1.66)	0.681
	Medium	299	92.6	6.0	1.3				
	High	299	93.0	5.7	1.3				
5	Low	300	94.7	4.7	0.7	1.13 (0.96,1.34)	0.150	1.08 (0.75,1.56)	0.668
	Medium	296	92.6	6.1	1.4				
	High	297	92.9	5.7	1.4				
6[c]	Low	299	94.7	4.7	0.7	1.14 (0.95,1.36)	0.151	1.11 (0.76,1.63)	0.584
	Medium	296	92.6	6.1	1.4				
	High	297	92.9	5.7	1.4				

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 20-11. (Continued)
Analysis of Loss of Vital Capacity

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED						
		Analysis Results for Log_2 (Current Dioxin + 1)				
		Mild vs. None		Moderate or Severe vs. None		
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	892	1.12 (0.90,1.40)**	0.297**	1.05 (0.62,1.78)**	0.852**	CURR*RACE (p=0.019) CURR*CSMOK (p=0.016) AGE (p=0.003) BFAT (p=0.002) RACE*PACKYR (p=0.026)
5	892	1.12 (0.93,1.36)**	0.229**	1.05 (0.67,1.66)**	0.826**	CURR*CSMOK (p=0.049) AGE (p=0.004) BFAT (p=0.003) RACE*PACKYR (p=0.034)
6[c]	891	1.15 (0.94,1.40)	0.187	1.05 (0.64,1.72)	0.839	CSMOK (p=0.067) AGE*BFAT (p=0.040) RACE*PACKYR (p=0.030)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

** Log_2 (current dioxin + 1)-by-covariate interaction ($0.01 < p \leq 0.05$); adjustive relative risk, confidence interval, and p-value derived from a model after deletion of this interaction; refer to Appendix Table P-2-7 for further analysis of this interaction.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

age, current cigarette smoking, body fat, industrial chemicals exposure, and a race-by-lifetime cigarette smoking history interaction.

All Model 2 and 3 unadjusted and adjusted analyses of the relationship of loss of vital capacity with initial dioxin were nonsignificant (Table 20-11(c-f): $p>0.19$). Analyses included contrasts between none and mild loss of vital capacity and between none and moderate or severe loss of vital capacity. Age, body fat, and a race-by-lifetime cigarette smoking history interaction were included in both models. Additionally, an occupation-by-industrial chemicals exposure interaction was significant for Model 2, and current cigarette smoking and industrial chemicals exposure were retained in Model 3.

Analysis of current dioxin versus loss of vital capacity proved nonsignificant for all unadjusted and adjusted contrasts examined for Models 4, 5, and 6 (Table 20-11(g,h): $p\geq0.15$ for all contrasts). Adjusted results presented in Table 20-11(h) for Models 4 and 5 are from the final model after significant covariate interactions involving current dioxin were deleted from the model. The current dioxin-by-race and current dioxin-by-current cigarette smoking interactions, as well as age, body fat, and a race-by-lifetime cigarette smoking history interaction exhibited significance in Model 4. A current dioxin-by-current cigarette smoking interaction, a race-by-lifetime cigarette smoking history interaction, age, and body fat displayed significant covariate effects in Model 5. Results stratified by each current dioxin-by-covariate level for Models 4 and 5 are presented in Appendix Table P-2-7. Model 6 was adjusted for current cigarette smoking and age-by-body fat and race-by-lifetime cigarette smoking history interactions. Also, as presented in Appendix Table P-3-9, when body fat was removed from the adjusted model for Models 4, 5, and 6, the positive association between loss of vital capacity for none versus mild becomes significant or marginally significant ($p<0.06$) for all three models.

Obstructive Abnormality

All group differences tested nonsignificant for both the unadjusted and adjusted analyses of obstructive abnormality (Table 20-12(a,b): $p>0.10$ for all contrasts). For the adjusted analysis of obstructive abnormality, the interaction between group and lifetime cigarette smoking history was significant (Table 20-12(b): $p=0.021$). Results stratified by levels of lifetime cigarette smoking history are presented in Appendix Table P-2-8. Results presented in Table 20-12(b) are the adjusted analysis results obtained after excluding this interaction from the model. Other significant effects included age, industrial chemicals exposure, and occupation-by-current cigarette smoking, occupation-by-lifetime cigarette smoking history, and body fat-by-current cigarette smoking interactions.

The unadjusted analysis of Model 2 revealed a significant decreased risk of mild obstructive abnormalities for increasing levels of initial dioxin (Table 20-12(c): $p=0.044$, Est. RR=0.86). However, after adjusting for industrial chemicals exposure and age-by-lifetime cigarette smoking history, current cigarette smoking by-body-fat, and lifetime cigarette smoking history-by-body fat interactions, Model 2 did not detect a significant association between initial dioxin and either of the obstructive abnormalities classifications. For the Model 3 unadjusted analysis, the associations between categorized dioxin and the obstructive abnormalities classifications were nonsignificant (Table 20-12(e): $p>0.13$ for all

Table 20-12.
Analysis of Obstructive Abnormality

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED										
			Percent			Mild vs. None		Moderate or Severe vs. None	
Occupational Category	Group	n	None	Mild	Mod. or Sev.	Est. Relative Risk (95% C.I.)	p-Value	Est. Relative Risk (95% C.I.)	p-Value
All	***Ranch Hand***	***951***	***55.5***	***36.8***	***7.7***	***1.06 (0.89,1.27)***	***0.493***	***1.21 (0.87,1.69)***	***0.256***
	Comparison	***1,280***	***57.5***	***35.9***	***6.6***				
Officer	Ranch Hand	366	51.9	40.7	7.4	1.11 (0.84,1.48)	0.454	1.31 (0.75,2.28)	0.335
	Comparison	502	55.2	38.8	6.0				
Enlisted Flyer	Ranch Hand	162	43.2	44.4	12.4	1.23 (0.80,1.91)	0.344	1.82 (0.88,3.77)	0.106
	Comparison	203	50.2	41.9	7.9				
Enlisted Groundcrew	Ranch Hand	423	63.3	30.5	6.2	0.96 (0.73,1.27)	0.786	0.91 (0.54,1.54)	0.737
	Comparison	575	62.3	31.1	6.6				

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED					
	Mild vs. None		Moderate or Severe vs. None		
Occupational Category	Adj. Relative Risk (95% C.I.)	p-Value	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks[a]
All	***1.17 (0.86,1.28)****	***0.624****	***1.05 (0.81,1.69)****	***0.396****	GROUP*PACKYR (p=0.021) AGE (p<0.001) IC (p=0.034) OCC*CSMOK (p=0.011) OCC*PACKYR (p=0.031) CSMOK*BFAT (p=0.002)
Officer	1.08 (0.79,1.47)**	0.638**	1.20 (0.65,2.21)**	0.552**	
Enlisted Flyer	1.24 (0.77,2.01)**	0.379**	1.77 (0.81,3.87)**	0.155**	
Enlisted Groundcrew	0.97 (0.71,1.31)**	0.821**	0.93 (0.53,1.65)**	0.809**	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

** Group-by-covariate interaction ($0.01 < p \leq 0.05$); relative risk, confidence interval, and p-value derived from a model after deletion of this interaction; refer to Appendix Table P-2-8 for further analysis of this interaction.

Table 20-12. (Continued)
Analysis of Obstructive Abnormality

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED								
Initial Dioxin Category Summary Statistics					Analysis Results for Log_2 (Initial Dioxin)[a]			
		Percent			Mild vs. None		Moderate or Severe vs. None	
Initial Dioxin Category	n	None	Mild	Mod. or Sev.	Est. Relative Risk (95% C.I.)[b]	p-Value	Est. Relative Risk (95% C.I.)[b]	p-Value
Low	174	51.2	40.2	8.6	0.86 (0.74,1.00)	0.044	0.80 (0.60,1.06)	0.115
Medium	173	57.8	32.9	9.3				
High	173	68.2	28.3	3.5				

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED					
Analysis Results for Log_2 (Initial Dioxin)[c]					
	Mild vs. None		Moderate or Severe vs. None		
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
520	0.98 (0.82,1.16)	0.795	0.97 (0.70,1.34)	0.850	IC (p=0.006) AGE*PACKYR (p=0.036) CSMOK*BFAT (p=0.031) PACKYR*BFAT (p=0.012)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 20-12. (Continued)
Analysis of Obstructive Abnormality

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED								
		Percent			Mild vs. None		Moderate or Severe vs. None	
Dioxin Category	n	None	Mild	Mod. or Sev.	Est. Relative Risk (95% C.I.)[ab]	p-Value	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,062	57.5	35.4	7.1				
Background RH	373	51.2	39.9	8.9	1.21 (0.94,1.56)	0.136	1.30 (0.83,2.03)	0.251
Low RH	260	55.0	36.2	8.8	1.08 (0.81,1.45)	0.604	1.29 (0.78,2.14)	0.328
High RH	260	63.1	31.5	5.4	0.85 (0.63,1.14)	0.268	0.74 (0.40,1.35)	0.321
Low plus High RH	520	59.0	33.9	7.1	0.96 (0.76,1.20)	0.701	1.00 (0.66,1.53)	0.987

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED						
		Mild vs. None		Moderate or Severe vs. None		
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	1,060					DXCAT*PACKYR (p=0.026) AGE (p<0.001) OCC*CSMOK (p=0.003) OCC*BFAT (p=0.010) CSMOK*BFAT (p=0.008) BFAT*IC (p=0.037)
Background RH	372	1.14 (0.86,1.51)**	0.360**	1.30 (0.78,2.16)**	0.307**	
Low RH	260	0.96 (0.70,1.32)**	0.822**	1.08 (0.62,1.89)**	0.785**	
High RH	260	1.05 (0.74,1.47)**	0.798**	0.85 (0.44,1.66)**	0.631**	
Low plus High RH	520	1.00 (0.78,1.29)**	0.997**	0.98 (0.62,1.56)**	0.938**	

[a] Relative risk and confidence interval relative to Comparisons.
[b] Adjusted for percent body fat at the time of duty in SEA and change in body fat from the time of duty in SEA to the date of the blood draw for dioxin.
[c] Adjusted for percent body fat at the time of duty in SEA, change in body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

** Categorized dioxin-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model after deletion of this interaction; refer to Appendix Table P-2-8 for further analysis of this interaction.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 20-12. (Continued)
Analysis of Obstructive Abnormality

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED									
	Current Dioxin Category Summary Statistics					Analysis Results for Log_2 (Current Dioxin + 1)			
			Percent			Mild vs. None		Moderate or Severe vs. None	
Model[a]	Current Dioxin Category	n	None	Mild	Mod. or Sev.	Est. Relative Risk (95% C.I.)[b]	p-Value	Est. Relative Risk (95% C.I.)[b]	p-Value
4	Low	295	50.5	41.0	8.5	0.84 (0.76,0.92)	<0.001	0.80 (0.67,0.96)	0.015
	Medium	299	53.2	38.1	8.7				
	High	299	63.6	30.1	6.4				
5	Low	300	51.7	40.3	8.0	0.88 (0.81,0.96)	0.003	0.84 (0.72,0.98)	0.022
	Medium	296	52.0	38.5	9.5				
	High	297	63.6	30.3	6.1				
6[c]	Low	299	51.8	40.1	8.0	0.86 (0.79,0.94)	0.001	0.83 (0.71,0.97)	0.018
	Medium	296	52.0	38.5	9.5				
	High	297	63.6	30.3	6.1				

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 20-12. (Continued)
Analysis of Obstructive Abnormality

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED						
	Analysis Results for Log_2 (Current Dioxin + 1)					
		Mild vs. None		Moderate or Severe vs. None		
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	892	0.88 (0.77,1.01)	0.061	0.86 (0.67,1.09)	0.206	AGE (p<0.001) PACKYR (p<0.001) RACE*IC (p=0.026) OCC*CSMOK (p=0.003) CSMOK*BFAT (p=0.004)
5	892	0.91 (0.82,1.02)	0.123	0.88 (0.72,1.08)	0.228	AGE (p<0.001) PACKYR (p<0.001) RACE*IC (p=0.026) OCC*CSMOK (p=0.003) CSMOK*BFAT (p=0.004)
6[d]	891	0.91 (0.81,1.03)	0.135	0.89 (0.72,1.11)	0.303	PACKYR (p<0.001) AGE*BFAT (p=0.003) RACE*IC (p=0.024) OCC*CSMOK (p=0.003) CSMOK*BFAT (p=0.004)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

analyses). Similar, nonsignificant results were found for the adjusted analysis for Model 3 (Table 20-12(f): $p>0.30$ for all contrasts). The adjusted Model 3 analysis detected a significant categorized dioxin-by-lifetime cigarette smoking history interaction (Table 20-12(f): $p=0.026$). Stratified analyses for this interaction are presented in Appendix Table P-2-8. The results presented in Table 20-12 for the adjusted analysis for Model 3 were derived after deletion of the categorized current dioxin-by-lifetime cigarette smoking history interaction. Model 3 was also adjusted for the covariates and interactions of age, occupation-by-current cigarette smoking, occupation-by-body fat, current cigarette smoking-by-body fat, and body fat-by-industrial chemicals exposure.

Each unadjusted analysis of Models 4 through 6 revealed a significant inverse association between obstructive abnormality and current dioxin for the contrasts of mild versus none and moderate or severe versus none (Table 20-12(g): $p\leq0.022$, Est. RR $\leq$ 0.88 for all analyses). However, after adjustment for covariate effects for each model, only the mild versus none contrast for Model 4 demonstrated a marginally significant association (Table 20-12(h): $p=0.061$, Est. RR=0.88). When body fat was excluded from the adjusted analysis of Models 4, 5, and 6, the inverse association between current dioxin and mild obstructive abnormalities became significant for all three models (Appendix Table P-3-10(c): $p\leq0.05$ for all analyses) and marginally significant for the relationship between current dioxin and moderate or severe abnormalities for Models 4 and 5. Significant effects for each model included lifetime cigarette smoking and race-by-industrial chemicals exposure, occupation-by-current cigarette smoking, current cigarette smoking-by-body fat interactions. Age was also significant for Models 4 and 5, and an age-by-body fat interaction was significant for Model 6.

Longitudinal Analysis

Longitudinal analyses were conducted on the ratio of observed FEV_1 to observed FVC to examine whether changes over time differed with respect to group membership (Model 1), initial dioxin (Model 2), and categorized dioxin (Model 3). Models 4, 5, and 6 were not examined in longitudinal analyses because current dioxin, the measure of exposure in these models, changes over time and is not available for all participants for 1982, 1985, or 1992. The longitudinal analyses for this variable investigated the difference between the measures for the 1982 examination and the 1992 examination. Summary statistics for the 1987 examination are provided for reference purposes. This measurement was not collected for the 1985 followup examination.

The longitudinal analysis for the ratio of observed FEV_1 to observed FVC examined the paired difference between the measurements for 1992 and 1982. These paired differences measured the change in the ratio over time. A logarithmic transformation was applied to 1 minus this ratio prior to calculating the paired differences for analysis purposes. Each of the three models used in the longitudinal analysis were adjusted for age and the dependent variable as measured in 1982 (see Statistical Methods, Chapter 7). The analyses of Models 2 and 3 also were adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

Laboratory Examination Variable

Ratio of Observed FEV_1 to Observed FVC

The Model 1 analysis of the change in the ratio of observed FEV_1 to observed FVC did not uncover a significant overall difference between Ranch Hands and Comparisons (Table 20-13(a): $p=0.420$). However, stratifying the Model 1 analysis by occupation detected a significant group difference for the enlisted flyers (Table 20-13(a): $p=0.021$). Of the enlisted flyers, the Ranch Hands had an examination mean change of -0.069 between 1992 and 1982, compared to -0.055 for the Comparisons.

The results for the Model 2 analysis did not reveal a significant association between the change in the ratio of observed FEV_1 to observed FVC and initial dioxin (Table 20-13(b): $p=0.374$). Similarly, the Model 3 analysis did not detect a significant relationship between the change in the ratio and categorized dioxin (Table 20-13(c): $p>0.37$ for all contrasts).

DISCUSSION

Although the presence of pulmonary disease may be apparent based on the history and physical examination, definitive diagnosis often requires the collection of laboratory data analyzed in the current section. In addition, because the lung is often involved secondarily in numerous infectious, inflammatory, and neoplastic disorders, the assessment of lung disease should include the type of comprehensive multisystem review conducted in these examinations and reported in other chapters.

Historical information on the occurrence of pulmonary disease must be interpreted with caution in the absence of medical record verification. Many of the cardinal symptoms of lung disease, including dyspnea, chest pain, and exercise intolerance, are common to cardiovascular disease as well (particularly ischemic heart disease) and are misinterpreted frequently as to cause. Wheezing, assumed by the patient to be indicative of asthma, may in fact be reflective of hemodynamic compromise in congestive heart failure. "Pneumonia" and "pneumonitis" are often confused by patients in relating the medical history. Thus, all episodes of pulmonary disease were verified by medical records and only verified occurrences were analyzed.

The physical examination variables studied can provide valuable clues to the presence of pulmonary disease; however, in lacking specificity, these data are limited in confirming a diagnosis. Wheezes and hyperresonance, for example, will occur in obstructive airway disease in asthma or in emphysema secondary to cigarette use. Dullness to percussion, a finding common to many disorders, will occur in consolidation from atelectasis, infections, pleural thickening, or pleural effusion.

In view of the limitations of the history and physical examination noted above, added emphasis is placed on screening laboratory data in the diagnosis of respiratory disease. The chest x ray, when normal, is highly reliable in excluding pulmonary parenchymal disease, though several exceptions must be recognized. Solitary lesions less than 6 millimeters, miliary granulomatous infection, and early interstitial disease, among others, may be present

Table 20-13.
Longitudinal Analysis of Ratio of Observed FEV_1 to Observed FVC

a) MODEL 1: RANCH HANDS VS. COMPARISONS							
		Mean[a]/(n) Examination					
Occupational Category	Group	1982	1987	1992	Exam. Mean Change[b]	Difference of Exam. Mean Change	p-Value[c]
All	***Ranch Hand***	***0.814 (900)***	***0.816 (868)***	***0.761 (900)***	***-0.054***	***-0.002***	***0.420***
	Comparison	***0.815 (1,060)***	***0.817 (1,034)***	***0.763 (1,060)***	***-0.052***		
Officer	Ranch Hand	0.806 (339)	0.809 (333)	0.751 (339)	-0.055	0.000	0.983
	Comparison	0.812 (403)	0.813 (391)	0.757 (403)	-0.055		
Enlisted Flyer	Ranch Hand	0.810 (159)	0.801 (153)	0.742 (159)	-0.069	-0.014	0.021
	Comparison	0.806 (173)	0.805 (172)	0.751 (173)	-0.055		
Enlisted Groundcrew	Ranch Hand	0.822 (402)	0.827 (382)	0.776 (402)	-0.047	0.001	0.798
	Comparison	0.820 (484)	0.285 (471)	0.772 (484)	-0.048		

[a] Transformed from natural logarithm of (1-X) scale.

[b] Difference between 1992 and 1982 examination means after transformation to original scale.

[c] P-value is based on analysis of natural logarithm of 1-ratio; results adjusted for natural logarithm of 1-ratio in 1982 and age in 1992.

Note: Summary statistics for 1987 are provided for reference purposes for participants who attended the Baseline, 1987, and 1992 examination. Data were not collected for the 1985 examination.

Table 20-13. (Continued)
Longitudinal Analysis of Ratio of Observed FEV_1 to Observed FVC

b) MODEL 2: RANCH HANDS — INITIAL DIOXIN					
	Initial Dioxin Category Summary Statistics Mean[a]/(n) Examination			Analysis Results for Log_2 (Initial Dioxin)[b]	
Initial Dioxin	1982	1987	1992	Adj. Slope (Std. Error)	p-Value
Low	0.815 (167)	0.817 (166)	0.759 (167)	-0.0031 (0.0034)	0.374
Medium	0.813 (169)	0.810 (165)	0.757 (169)		
High	0.834 (168)	0.842 (162)	0.792 (168)		

[a] Transformed from natural logarithm of (1-X) scale.

[b] Results based on difference between natural logarithm of 1-ratio in 1992 and natural logarithm of 1-ratio in 1982 versus $\log_2$ (initial dioxin); results adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, natural logarithm of 1-ratio in 1982, and age in 1992.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.
Summary statistics for 1987 are provided for reference purposes for participants who attended the Baseline, 1987, and 1992 examinations. Data were not collected for the 1985 examination.

Table 20-13. (Continued)
Longitudinal Analysis of Ratio of Observed FEV_1 to Observed FVC

c) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY						
	Mean[a]/(n) Examination					
Dioxin Category	1982	1987	1992	Exam. Mean Change[b]	Difference of Exam. Mean Change	p-Value[c]
Comparison	0.815 (914)	0.817 (904)	0.763 (914)	-0.052		
Background RH	0.804 (341)	0.804 (334)	0.746 (341)	-0.058	-0.007	0.378
Low RH	0.817 (250)	0.816 (248)	0.762 (250)	-0.056	-0.004	0.590
High RH	0.825 (254)	0.831 (245)	0.778 (254)	-0.047	0.005	0.743
Low plus High RH	0.821 (504)	0.823 (493)	0.770 (504)	-0.051	0.001	0.577

[a] Transformed from natural logarithm of (1-X) scale.

[b] Difference between 1992 and 1982 examination means after transformation to original scale.

[c] P-value is based on analysis of natural logarithm of 1-ratio; results adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, natural logarithm of 1-ratio in 1982, and age in 1992.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Summary statistics for 1987 are provided for reference purposes for participants who attended the Baseline, 1987, and 1992 examinations. Data were not collected for the 1985 examination.

but not detectable radiographically. Furthermore, it is recognized clinically that the chest x ray is not sensitive to the detection of obstructive airway disease in an early stage. On the other hand, the chest x ray may reveal an early occult malignancy in an asymptomatic patient and afford a rare opportunity for cure.

Spirometry has been used as a clinical tool to measure static lung volumes and to detect respiratory disease for more than a century. Dynamic indices, relating changes in lung volume to time, were first developed more than 50 years ago and, with computerization, have been refined to a high degree of accuracy and reproducibility. To be valid, spirometry requires that particular attention be paid to technician training and to eliciting the full cooperation of the patient. In spirometry, a premium is placed on using identical techniques in longitudinal studies. These factors received special emphasis in this study.

The spirometric indices evaluated in this chapter are designed to measure lung volume (FVC) and respiratory air flow (FEV_1). Static lung volume is principally determined by height and is independent of weight, while dynamic volume measurements depend in part on physical strength. Accordingly, all indices require correction for age and height. In the current study, an apparent increase in the FEV_1 to FVC ratio was driven more by a reduction in the static index, FVC, associated with restrictive or infiltrative lung disease, than by any significant changes in the dynamic index, FEV_1.

Respiratory disease may be divided into two general categories in clinical practice. "Restrictive" disease is characterized by reduced vital capacity as seen in interstitial fibrosis or reduced lung volume postsurgical resection. In "obstructive" airways disease associated with cigarette use (usually chronic obstructive pulmonary disease), the flow-dependent index, FEV_1, is abnormally prolonged.

The analyses of dependent variable-covariate associations confirm observations that are well established in clinical practice. Lifetime cigarette smoking history was a highly significant risk factor with respect to the development of bronchitis and pneumonia and for all of the laboratory indices analyzed. Of interest, over the 10-year course of these examinations, the percentage of participants has steadily decreased from 42 percent in 1982 to 25 percent in 1992. Stratification by occupation confirms that, as a group, officers are significantly less likely to develop lung disease than enlisted personnel. With advancing age, an increase in respiratory disease was confirmed by history and on physical examination, as was an age-related decline in the static and dynamic indices of pulmonary function. Related to racial variations in body habitus, Blacks have a slight reduction in vital capacity relative to non-Blacks. Finally, the analyses of body fat confirmed the well-recognized reduction in vital capacity and its derivatives associated with obesity.

The analyses of historical variables yielded inconsistent results. Bronchitis was more common and pneumonia less common in Ranch Hands than in Comparisons. Of interest, but of uncertain cause, Ranch Hand enlisted flyers appeared to be at selective risk relative to Comparisons with respect to the history of bronchitis (19.4% vs. 16.6%) and the frequency of abnormalities noted on physical examination (22.8% vs. 12.3%) and chest x ray (19.1% vs. 14.3%). There was, however, no evidence for any relationship with the current body burden of dioxin.

Although in the analyses of static and dynamic laboratory variables, no significant group differences were defined, within the Ranch Hand cohort there was evidence for a dioxin effect similar to that documented in the 1987 examinations and the subsequent serum dioxin analysis. A slight reduction in FVC was noted in those participants with high versus low extrapolated initial dioxin and in all models employing current serum dioxin as well. Similar directional changes were noted in the FVC derived index of the ratio of observed FEV_1 to observed FVC. Although consistent with a dose-response effect, the differences in the means were slight and of doubtful physiologic significance. Clinically, a reduction in FVC is noted often in obese patients, and these results may reflect in part the strong positive association between current serum dioxin and body fat noted in Chapter 9, General Health.

Longitudinal analyses of the ratio of observed FEV_1 to observed FVC did not reveal any significant differences between the Ranch Hand and Comparison cohorts. In the enlisted flyer category, Ranch Hands had a slightly greater reduction in the ratio than did Comparisons, but the difference (-0.069 vs. -0.055) is not physiologically significant. There was no evidence for any trend in relation to the extrapolated initial or current serum dioxin levels.

In summary, the historical, physical examination, and laboratory data analyzed revealed no evidence for an increase in pulmonary disease in the Ranch Hand cohort relative to the Comparisons. Selected results were consistent with a subtle dose-response effect related to dioxin exposure, although body habitus—and more specifically, body fat—may play a role in these associations.

SUMMARY

The Pulmonary Assessment comprised analyses of the following health endpoints: the occurrence (after duty in SEA) of asthma, bronchitis, and pneumonia; thorax and lung abnormalities; x ray interpretation; FVC (percent of predicted); FEV_1 (percent of predicted); ratio of observed FEV_1 to observed FVC; loss of vital capacity; and obstructive abnormality. Statistical examinations were performed for each variable with group (Model 1), initial dioxin (Model 2), categorized dioxin (Model 3), current lipid-adjusted dioxin (Model 4), and current whole-weight dioxin (Models 5 and 6). Summarized results are presented in Tables 20-14 through 20-17. A summary of group-by-covariate and dioxin-by-covariate interactions is provided in Table 20-18.

Model 1: Group Analysis

The history of bronchitis differed significantly between Ranch Hand and Comparison enlisted flyers for both the Model 1 unadjusted and adjusted analyses ($p=0.037$ and $p=0.033$ respectively), with a higher percentage of enlisted flyer Ranch Hands than enlisted flyer Comparisons having a history of post-SEA bronchitis. Similar results were found for thorax and lung abnormalities. Ranch Hand enlisted flyers exhibited a significantly higher percentage of thorax and lung abnormalities than did Comparison enlisted flyers ($p=0.012$ unadjusted and $p=0.021$ adjusted). In addition, the history of pneumonia differed significantly between groups across all occupations for both the unadjusted and adjusted analyses ($p=0.012$ and $p=0.008$ respectively); however, a higher percentage of Comparisons

Table 20-14.
Summary of Group Analyses (Model 1) for Pulmonary Variables
(Ranch Hands vs. Comparisons)

	UNADJUSTED			
Variable	**All**	**Officer**	**Enlisted Flyer**	**Enlisted Groundcrew**
Verified Medical Records				
Asthma (D)	NS	NS	ns	NS
Bronchitis (D)	NS*	NS	+0.037	NS
Pneumonia (D)	-0.012	-0.029	NS	ns
Physical Examination				
Thorax and Lung Abnormalities (D)	+0.011	NS	+0.012	NS
Laboratory				
X Ray Interpretation (D)	NS	ns	NS	ns
FVC[a] (C)	ns	ns	NS	ns
FEV_1[a] (C)	ns	ns	ns	ns
Ratio of Observed FEV_1 to Observed FVC[a] (C)	ns	ns	ns	NS
Loss of Vital Capacity[b] (D)	ns	ns	ns*	ns
Loss of Vital Capacity[c] (D)	ns	NS	ns	ns
Obstructive Abnormality[b] (D)	NS	NS	NS	ns
Obstructive Abnormality[c] (D)	NS	NS	NS	ns

[a] Negative difference considered adverse for this variable.
[b] Mild contrasted with none.
[c] Moderate or severe contrasted with none.
C: Continuous analysis.
D: Discrete analysis.
+: Relative risk $\geq$ 1.00.
-: Relative risk $<$ 1.00.
NS or ns: Not significant ($p>0.10$).
NS* or ns*: Marginally significant ($0.05<p\leq0.10$).
Note: P-value given if $p\leq0.05$.
A capital "NS" denotes a relative risk 1.00 or greater for discrete analysis or difference of means nonnegative for continuous analysis; a lower case "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis.

Table 20-14. (Continued)
Summary of Group Analyses (Model 1) for Pulmonary Variables
(Ranch Hands vs. Comparisons)

	ADJUSTED			
Variable	All	Officer	Enlisted Flyer	Enlisted Groundcrew
Verified Medical Records				
Asthma (D)	NS	--	--	--
Bronchitis (D)	NS*	ns	+0.033	NS
Pneumonia (D)	-0.008	-0.017	ns	ns*
Physical Examination				
Thorax and Lung Abnormalities (D)	+0.033	NS	+0.021	NS
Laboratory				
X Ray Interpretation (D)	ns	ns	NS	ns
FVC[a] (C)	ns	ns	NS	ns
FEV_1[a] (C)	ns	ns	ns	ns
Ratio of Observed FEV_1 to Observed FVC[a] (C)	ns	ns	ns	NS
Loss of Vital Capacity[b] (D)	ns	ns	-0.048	NS
Loss of Vital Capacity[c] (D)	ns	NS	ns	ns
Obstructive Abnormality[b] (D)	**(NS)	**(NS)	**(NS)	**(ns)
Obstructive Abnormality[c] (D)	**(NS)	**(NS)	**(NS)	**(ns)

[a] Negative difference considered adverse for this variable.
[b] Mild contrasted with none.
[c] Moderate or severe contrasted with none.
C: Continuous analysis.
D: Discrete analysis.
+: Relative risk ≥ 1.00.
-: Relative risk < 1.00.
--: Analysis not performed due to sparse number of abnormalities.
NS or ns: Not significant ($p>0.10$).
NS* or ns*: Marginally significant ($0.05<p\leq0.10$).
**(NS) or **(ns): Group-by-covariate interaction ($p\leq0.05$); not significant when interaction is deleted; refer to Appendix P-2 for further analysis of this interaction.
Note: A capital "NS" denotes a relative risk 1.00 or greater for discrete analysis or difference of means nonnegative for continuous analysis; a lower case "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis.

Table 20-15.
Summary of Initial Dioxin Analyses (Model 2) for Pulmonary Variables (Ranch Hands Only)

Variable	Unadjusted	Adjusted
Verified Medical Records		
Asthma (D)	NS	NS
Bronchitis (D)	NS	NS
Pneumonia (D)	ns	ns
Physical Examination		
Thorax and Lung Abnormalities (D)	NS	NS
Laboratory		
X Ray Interpretation (D)	ns	ns
FVC[a] (C)	ns	-0.034
FEV_1[a] (C)	NS	****
Ratio of Observed FEV_1 to Observed FVC[ab] (C)	+0.008	NS
Loss of Vital Capacity[c] (D)	NS	NS
Loss of Vital Capacity[d] (D)	ns	ns
Obstructive Abnormality[c] (D)	-0.044	ns
Obstructive Abnormality[d] (D)	ns	ns

[a] Negative slope considered adverse for this variable.
[b] Positive association between variable and $\log_2$ (initial dioxin); however, slope is negative in analysis due to natural logarithm (1-X) transformation; directionality of association in table is opposite of analysis slope.
[c] Mild contrasted with none.
[d] Moderate or severe contrasted with none.
C: Continuous analysis.
D: Discrete analysis.
+: Slope negative for variable; however, due to transformation used in analysis, directionality of association is positive.
-: Relative risk < 1.00; slope negative for continuous analysis.
NS or ns: Not significant ($p>0.10$).
**** Log_2 (initial dioxin)-by-covariate interaction ($p \leq 0.01$); refer to Appendix P-2 for further analysis of this interaction.
Note: P-value given if $p \leq 0.05$.
A capital "NS" denotes a relative risk 1.00 or greater for discrete analysis or slope nonnegative for continuous analysis; a lower case "ns" denotes relative risk less than 1.00 for discrete analysis or slope negative for continuous analysis, except as noted above for the ratio of observed FEV_1 to observed FVC.

Table 20-16.
Summary of Categorized Dioxin Analyses (Model 3) for Pulmonary Variables (Ranch Hands vs. Comparisons)

	UNADJUSTED			
Variable	Background Ranch Hands vs. Comparisons	Low Ranch Hands vs. Comparisons	High Ranch Hands vs. Comparisons	Low plus High Ranch Hands vs. Comparisons
Verified Medical Records				
Asthma (D)	NS	NS	NS	NS
Bronchitis (D)	NS	NS	NS	NS
Pneumonia (D)	ns	ns*	-0.008	-0.002
Physical Examination				
Thorax and Lung Abnormalities (D)	+0.028	NS	NS*	NS
Laboratory				
X Ray Interpretation (D)	NS	ns	ns	ns
FVC[a] (C)	NS	ns	ns	ns*
FEV_1[a] (C)	ns	ns	ns	ns
Ratio of Observed FEV_1 to Observed FVC[a] (C)	-0.009	NS	+0.022	NS
Loss of Vital Capacity[b] (D)	ns	ns	ns	ns
Loss of Vital Capacity[c] (D)	ns	NS	ns	ns
Obstructive Abnormality[b] (D)	NS	NS	ns	ns
Obstructive Abnormality[c] (D)	NS	NS	ns	NS

[a] Negative difference considered adverse for this variable.
[b] Mild contrasted with none.
[c] Moderate or severe contrasted with none.
C: Continuous analysis.
D: Discrete analysis.
+: Relative risk ≥ 1.00 for discrete analysis or difference of means nonnegative for continuous analysis.
-: Relative risk < 1.00 for discrete analysis or difference of means negative for continuous analysis.
NS or ns: Not significant ($p>0.10$).
NS* or ns*: Marginally significant ($0.05<p\leq0.10$).
Note: P-value given if $p\leq0.05$.
A capital "NS" denotes a relative risk 1.00 or greater for discrete analysis or difference of means nonnegative for continuous analysis; a lower case "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis.

Table 20-16. (Continued)
Summary of Categorized Dioxin Analyses (Model 3) for Pulmonary Variables (Ranch Hands vs. Comparisons)

	ADJUSTED			
Variable	Background Ranch Hands vs. Comparisons	Low Ranch Hands vs. Comparisons	High Ranch Hands vs. Comparisons	Low plus High Ranch Hands vs. Comparisons
Verified Medical Records				
Asthma (D)	NS	NS	NS	NS
Bronchitis (D)	+0.036	ns	ns	ns
Pneumonia (D)	ns	-0.038	-0.012	-0.002
Physical Examination				
Thorax and Lung Abnormalities (D)	+0.011	NS	NS	NS
Laboratory				
X Ray Interpretation (D)	**(NS)	**(ns)	**(ns)	**(ns)
FVC[a] (C)	NS	ns	ns	ns
FEV_1[a] (C)	ns	ns	ns	ns
Ratio of Observed FVC to Observed FEV_1[a] (C)	**(ns*)	**(NS)	**(NS)	**(NS)
Loss of Vital Capacity[b] (D)	ns	ns	ns	ns
Loss of Vital Capacity[c] (D)	ns	ns	ns	ns
Obstructive Abnormality[b] (D)	**(NS)	**(ns)	**(NS)	**(NS)
Obstructive Abnormality[c] (D)	**(NS)	**(NS)	**(ns)	**(ns)

[a] Negative difference considered adverse for this variable.
[b] Mild contrasted with none.
[c] Moderate or severe contrasted with none.
C: Continuous analysis.
D: Discrete analysis.
+: Relative risk $\geq$ 1.00.
-: Relative risk $<$ 1.00.
NS or ns: Not significant ($p>0.10$).
**(NS) or **(ns): Categorized dioxin-by-covariate interaction ($p\leq0.05$); not significant when interaction is deleted; refer to Appendix P-2 for further analysis of this interaction.
**(ns*): Categorized dioxin-by-covariate interaction ($p\leq0.05$); marginally significant when interaction is deleted; refer to Appendix P-2 for further analysis of this interaction.
Note: P-value given if $p\leq0.05$.
A capital "NS" denotes a relative risk 1.00 or greater for discrete analysis or difference of means nonnegative for continuous analysis; a lower case "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis.

Table 20-17.
Summary of Current Dioxin Analyses (Models 4, 5, and 6) for Pulmonary Variables (Ranch Hands Only)

	UNADJUSTED		
Variable	Model 4: Lipid-Adjusted Current Dioxin	Model 5: Whole-Weight Current Dioxin	Model 6: Whole-Weight Current Dioxin Adjusted for Total Lipids
Verified Medical Records			
Asthma (D)	NS	NS	NS
Bronchitis (D)	ns	ns	ns*
Pneumonia (D)	ns	ns	ns
Physical Examination			
Thorax and Lung Abnormalities (D)	ns	ns	ns
Laboratory			
X Ray Interpretation (D)	ns	ns	ns
FVC[a] (C)	-0.002	-0.001	-0.015
FEV_1[a] (C)	NS	NS	NS
Ratio of Observed FEV_1 to Observed FVC[ab] (C)	+<0.001	+<0.001	+<0.001
Loss of Vital Capacity[c] (D)	NS	NS	NS
Loss of Vital Capacity[d] (D)	NS	NS	NS
Obstructive Abnormality[c] (D)	-<0.001	-0.003	-0.001
Obstructive Abnormality[d] (D)	-0.015	-0.022	-0.018

[a] Negative slope considered adverse for this variable.
[b] Positive association between variable and $\log_2$ (current dioxin + 1); however, slope is negative in analysis due to natural logarithm (1-X) transformation; directionality of association in table is opposite of analysis slope.
[c] Mild contrasted with none.
[d] Moderate or severe contrasted with none.
C: Continuous analysis.
D: Discrete analysis.
+: Slope negative for variable; however, due to transformation used in analysis, directionality of association is positive.
-: Relative risk < 1.00 for discrete analysis; slope negative for continuous analysis.
NS or ns: Not significant.
ns*: Marginally significant ($0.05 < p \leq 0.10$).
Note: P-value given if $p \leq 0.05$.
A capital "NS" denotes a relative risk of 1.00 or greater for discrete analysis or slope nonnegative for continuous analysis; a lower case "ns" denotes relative risk less than 1.00 for discrete analysis or slope negative for continuous analysis, except as noted above for the ratio of observed FEV_1 to observed FVC.

Table 20-17. (Continued)
Summary of Current Dioxin Analyses (Models 4, 5, and 6) for Pulmonary Variables (Ranch Hands Only)

Variable	ADJUSTED		
	Model 4: Lipid-Adjusted Current Dioxin	Model 5: Whole-Weight Current Dioxin	Model 6: Whole-Weight Current Dioxin Adjusted for Total Lipids
Verified Medical Records			
Asthma (D)	**(NS)	ns	**(NS)
Bronchitis (D)	**(-0.011)	**(-0.031)	**(-0.004)
Pneumonia (D)	ns*	ns	ns
Physical Examination			
Thorax and Lung Abnormalities (D)	**(ns)	ns	ns
Laboratory			
X Ray Interpretation (D)	****	**(ns)	**(ns*)
FVC[a] (C)	ns	ns	ns
FEV_1[a] (C)	NS	NS	NS
Ratio of Observed FEV_1 to Observed FVC[ab] (C)	+0.001	+0.001	+0.001
Loss of Vital Capacity[c] (D)	**(NS)	**(NS)	NS
Loss of Vital Capacity[d] (D)	**(NS)	**(NS)	NS
Obstructive Abnormality[c] (D)	ns*	ns	ns
Obstructive Abnormality[d] (D)	ns	ns	ns

[a] Negative slope considered adverse for this variable.
[b] Positive association between variable and $\log_2$ (current dioxin + 1); however, slope is negative in analysis due to natural logarithm (1-X) transformation; directionality of association in table is opposite of analysis slope.
[c] Mild contrasted with none.
[d] Moderate or severe contrasted with none.
C: Continuous analysis.
D: Discrete analysis.
+: Slope nonnegative for variable; however due to transformation used in analysis, directionality of association is positive.
-: Relative risk < 1.00.
NS or ns: Not significant.
ns*: Marginally significant ($0.05 < p \leq 0.10$).
**(NS): $\log_2$ (current dioxin)-by-covariate interaction ($p \leq 0.05$); not significant when interaction is deleted; refer to Appendix P-2 for further analysis of this interaction.
**(ns*): $\log_2$ (current dioxin + 1)-by-covariate interaction ($0.01 < p \leq 0.05$); marginally significant when interaction is deleted; refer to Appendix P-2 for further analysis of this interaction.
**(...): $\log_2$ (current dioxin + 1)-by-covariate interaction ($0.01 < p \leq 0.05$); significant when interaction is deleted and p-value given in parentheses; refer to Appendix P-2 for further analysis of this interaction.
**** $\log_2$ (current dioxin + 1)-by-covariate interaction ($p \leq 0.01$); refer to Appendix P-2 for further analysis of this interaction.
Note: P-value given if $p \leq 0.05$.
A capital "NS" denotes a relative risk of 1.00 or greater for discrete analysis or a nonnegative slope for continuous analysis; a lower case "ns" denotes relative risk less than 1.00 for discrete analysis or slope negative for continuous analysis, except as noted above for the ratio of observed FEV_1 to observed FVC.

Table 20-18.
Summary of Group-by-Covariate and Dioxin-by-Covariate Interactions from Adjusted Analyses of Pulmonary Variables

Model	Variable	Covariate
1[a]	Obstructive Abnormality (D)	Lifetime Cigarette Smoking History
2[b]	FEV_1 (C)	Current Cigarette Smoking
3[c]	X Ray Interpretation (D)	Occupation
	Ratio of Observed FEV_1 to Observed FVC (C)	Age
	Obstructive Abnormality (D)	Lifetime Cigarette Smoking History
4[d]	Asthma (D)	Age
	Bronchitis (D)	Industrial Chemicals Exposure
	Thorax and Lung Abnormalities (D)	Current Cigarette Smoking
	X Ray Interpretation (D)	Current Cigarette Smoking
	Loss of Vital Capacity (D)	Race, Current Cigarette Smoking
5[e]	Bronchitis (D)	Industrial Chemicals Exposure
	X Ray Interpretation (D)	Current Cigarette Smoking
	Loss of Vital Capacity (D)	Current Cigarette Smoking
6[f]	Asthma (D)	Age
	Bronchitis (D)	Industrial Chemicals Exposure
	X Ray Interpretation (D)	Current Cigarette Smoking

C: Continuous analysis.
D: Discrete analysis.
[a] Group Analysis (Ranch Hands vs. Comparison).
[b] Ranch Hands—Log_2 (Initial Dioxin).
[c] Categorized Dioxin.
[d] Ranch Hands—Log_2 (Current Lipid-Adjusted Dioxin + 1).
[e] Ranch Hands—Log_2 (Current Whole-Weight Dioxin + 1).
[f] Ranch Hands—Log_2 (Current Whole-Weight Dioxin + 1), Adjusted for Total Lipids.

than Ranch Hands had a history of post-SEA pneumonia. Results are analogous for the officer stratum for the analysis of pneumonia ($p=0.029$ unadjusted and $p=0.017$ adjusted). The unadjusted analysis of loss of vital capacity, mild versus none, revealed marginally significant results for enlisted flyers, and the adjusted analysis displayed significant differences. Both analyses showed lower percentages of mild loss of vital capacity for the Ranch Hands than for the Comparisons. The adjusted analysis of obstructive abnormalities revealed a significant interaction between group and lifetime cigarette smoking history.

In the longitudinal analysis, the change in the ratio of observed FEV_1 to observed FVC between 1982 and 1992 differed significantly for enlisted flyers ($p=0.021$). The ratio decreased, and the change in the ratio was significantly greater for Ranch Hands than for Comparisons.

Model 2: Initial Dioxin Analysis

For the Model 2 unadjusted analyses, significant inverse associations were revealed between initial dioxin and the ratio of observed FEV_1 and observed FVC and mild obstructive abnormalities ($p=0.008$ and $p=0.044$ respectively). However, after adjusting for significant covariates, these associations were no longer significant. The adjusted analyses did find a significant association between initial dioxin and FVC ($p=0.034$). The negative association between dioxin and FVC is indicative of an adverse health effect for increasing levels of dioxin.

Model 3: Categorized Dioxin Analysis

Contrasts involving dioxin measurements on Ranch Hands and Comparisons were examined in the analysis of Model 3. The adjusted analysis of post-SEA bronchitis showed a significantly higher percentage of background Ranch Hands than Comparisons with a history of bronchitis ($p=0.036$). The unadjusted analysis of post-SEA pneumonia revealed a significantly higher percentage of Comparisons than Ranch Hands in the high and low plus high initial dioxin categories had a history of post-SEA pneumonia ($p=0.008$ and $p=0.002$ respectively). After adjustment for covariate effects, the differences remained significant for the high and low plus high categories and also were significant for the low Ranch Hands versus Comparisons, where a higher percentage of Comparisons than Ranch Hands in the low dioxin category had a history of post-SEA pneumonia. For the unadjusted and adjusted analyses of thorax and lung abnormalities, the background Ranch Hands exhibited a significantly higher percentage of thorax and lung abnormalities than the Comparisons ($p=0.028$ and $p=0.011$ respectively). The background Ranch Hand and high Ranch Hand contrasts for the unadjusted analysis of the ratio of observed FEV_1 to observed FVC were significant ($p=0.009$ and $p=0.022$ respectively). However, after adjusting for covariates, these contrasts were no longer significant.

Models 4, 5, and 6: Current Dioxin Analyses

Current dioxin effects upon pulmonary health variables were analyzed in Models 4 through 6. The adjusted analyses of post-SEA bronchitis revealed a significant inverse association between the history of bronchitis and current dioxin ($p=0.011$, $p=0.031$, and

p=0.004 respectively). For Models 4, 5, and 6, the analyses of x ray interpretation revealed a significant current dioxin-by-current cigarette smoking interaction. Model 6 revealed a marginally significant association between x ray interpretation and current dioxin after removal of the interaction from the final model. The unadjusted analysis of FVC exhibited a significant inverse association with current dioxin for Models 4 through 6; however, after adjusting for significant covariates, the analyses were no longer significant. The unadjusted and adjusted analyses of the ratio of observed FEV_1 to observed FVC both exhibited highly significant positive associations with current dioxin for Models 4 through 6 ($p \leq 0.001$ for all analyses). This relationship between the ratio and current dioxin could be indicative of a positive health effect; however, the increase in the FEV_1 to FVC ratio as dioxin increases appears to be driven by the significant decrease in FVC for increasing dioxin levels. Unadjusted analyses of obstructive abnormality for Models 4 through 6 each revealed a significant inverse association with current dioxin ($p \leq 0.022$ for all contrasts). However, after adjustment for covariates, only the Model 4 mild versus none contrast remained marginally significant.

CONCLUSION

For the medical records and physical examination pulmonary variables, the group analysis revealed significant relationships for bronchitis and thorax and lung abnormalities only. For enlisted flyers, significantly more Ranch Hands than Comparisons had post-SEA bronchitis and thorax and lung abnormalities. However, the initial dioxin, categorized dioxin, and current dioxin analyses for these variables did not confirm a dioxin dose-response relationship.

For the laboratory variables, a statistically significant inverse relationship was revealed between percent of predicted FVC and initial and current dioxin for Ranch Hands. However, when Ranch Hands were contrasted with Comparisons, no significant differences were detected. Also, the analysis of the ratio of observed FEV_1 to observed FVC within Ranch Hands revealed a significant direct relationship with initial dioxin indicating that the ratio increases (becomes closer to 1) for increasing levels of initial dioxin, which may be due to the diminishing magnitude of FVC in the denominator of the ratio.

In the longitudinal analysis of the ratio of observed FEV_1 to observed FVC, there was a significant group difference for the enlisted flyers. The Ranch Hand enlisted flyers had a larger decrease in the ratio between 1982 and 1992 than the Comparison enlisted flyers.

In summary, the historical, physical examination, and laboratory data analyzed for the Pulmonary Assessment revealed no consistent evidence of an increased prevalence of pulmonary disease in the Ranch Hand cohort in relation to body burden of dioxin.

CHAPTER 20
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CHAPTER 21

CONCLUSIONS

INTRODUCTION

This section summarizes the conclusions drawn from the statistical analyses of data from the 1992 followup examination of the Air Force Health Study (AFHS). The 1992 followup was an extension of the Baseline, 1985, and 1987 followup examinations. Health endpoints measured at the 1992 examination were analyzed for associations with dioxin (TCDD) exposure and body burden of serum dioxin, and were examined longitudinally in relation to data from the previous examination cycles.

STUDY PERFORMANCE ASPECTS

Participation at the 1992 followup examination remained high. Of the 1,148 eligible Ranch Hands, 952 participated in the 1992 followup examination, while 912 of the 1,191 eligible Comparisons from the Baseline examination participated in the 1992 followup. Of the 571 Comparisons identified as replacements for Original Comparisons, 369 participated in the 1992 followup. Ninety-one percent of living Ranch Hands and 92 percent of living Comparisons who were fully compliant at the Baseline examination returned for the 1992 followup examination. Each of the 952 Ranch Hands and 1,281 Comparisons at the 1992 followup completed the physical examination, but two participants refused to complete the questionnaire. Despite requirements in the Study Protocol, 62 of 279 noncompliant Comparisons were not replaced as they should have been. However, the total number of fully compliant participants would have increased by less than 3 percent and any biasing effect is considered negligible.

POPULATION CHARACTERISTICS

Overall, Ranch Hands and Comparisons had similar personal characteristics and lifestyle habits. However, notable exceptions included duration of combat service, reported herbicide exposure, and high-density lipoprotein (HDL). Ranch Hands tended to serve in combat longer than Comparisons, because Ranch Hands were stationed in combat areas for their entire time of duty in Southeast Asia (SEA), whereas Comparisons returned to stations outside of combat areas between missions. A possible explanation for a greater percentage of Ranch Hands than Comparisons reporting herbicide exposure may have been the tendency of Ranch Hands to report their exposure during their time of duty in SEA, although the questionnaire was designed to capture post-SEA exposure only. The relationship between group and HDL is not clear—the group means are not significantly different, but the percentage of Ranch Hands considered abnormal (less than 35 mg/dl) is significantly greater than the percentage of Comparisons. In Ranch Hands, most of the significant associations between dioxin and the covariates can be attributed to, or partially explained by, the effects of occupation, age, or body fat.

STATISTICAL MODELS

The analysis of the 1992 followup examination results employed six statistical models to evaluate the relationship between the health status of study participants and their dioxin exposure and serum dioxin levels. The first model specifies contrasts between Ranch Hands and Comparisons using group as a proxy for exposure and does not incorporate serum dioxin measurements. The remaining five models all incorporate serum dioxin measurements in either current or initial form. The six models are summarized as follows:

- Model 1: Ranch Hands versus Comparisons
- Model 2: Estimated initial serum dioxin levels using Ranch Hand participants with greater than 10 ppt of current lipid-adjusted dioxin
- Model 3: Ranch Hands categorized according to serum dioxin levels versus Comparisons with 10 ppt of current lipid-adjusted dioxin or less
- Model 4: Current lipid-adjusted serum dioxin using Ranch Hands only
- Model 5: Current whole-weight serum dioxin using Ranch Hands only
- Model 6: Current whole-weight serum dioxin, adjusted for total lipids, using Ranch Hands only.

In Model 1, the use of group and occupation as a surrogate for exposure is not subject to the possible biases based on health conditions that can occur with serum dioxin estimates. However, an implicit underlying assumption is that Ranch Hands were exposed and Comparisons were not exposed. Model 2 is based on initial dioxin levels that were extrapolated from current lipid-adjusted dioxin measurements above background levels (10 ppt), assuming first-order kinetics and a constant dioxin decay rate. Model 3 is less dependent on the accuracy of the initial dioxin estimation algorithm, but all Ranch Hands with high serum dioxin levels are treated alike without emphasizing the unusually large dioxin doses received by some Ranch Hands. Models 4, 5, and 6 are based on current dioxin measurements from the 1987 examination and assume nothing about dioxin elimination other than that Ranch Hands were exposed in Vietnam and their body-burdens have decreased over time in an unspecified manner. However, current dioxin may not be a good surrogate for exposure if elimination rates differ among individuals.

Statistical analyses often were applied to clinical endpoints in continuous form (i.e., original measurements) as well as in discrete form (i.e., measurements grouped into categories based on abnormal levels). Analyses also were performed to account for the effects that demographic and personal characteristics may have had on the clinical measurements. Such analyses are termed "adjusted analyses."

CLINICAL RESULTS

This section provides the conclusions from the analyses of the twelve clinical areas—general health, neoplasia, neurology, psychology, gastrointestinal, dermatology, cardiovascular, hematology, renal, endocrine, immunology, and pulmonary. Appendix Tables Q-1-1 through Q-1-24 of Appendix Q-1 present the results for each of the six models for more than 300 health endpoints analyzed in the 12 clinical chapters. Appendix Q-2 presents graphical displays of 26 selected continuous health measurements versus the logarithm (base 2) of current lipid-adjusted serum dioxin. These graphics represent scatterplots, unadjusted for any covariates, of the data used in Model 4 analyses.

General Health Assessment

General health was assessed by five measures, selected for sensitivity to the overall state of health rather than specific to any organ system; the five measures were: self-perception of health, appearance of illness or distress as assessed by a physician, relative age as assessed by a physician, percent body fat, and sedimentation rate.

At the 1992 examination, Ranch Hands perceived themselves as less healthy than Comparisons, just as they had at the 1982 and 1985 examinations (though not at the 1987 examination). Enlisted groundcrew, who experienced the highest levels of dioxin exposure, were particularly inclined to view their health negatively. A highly significant association between the current level of serum dioxin and a negative self-perception of health also was found in Ranch Hands. Because participants were aware of their serum dioxin levels, the possibility of bias in these results should be considered. Participants who knew they possessed an elevated dioxin level, or whose occupation implied a greater risk for exposure (i.e., enlisted groundcrew), may have consciously or subconsciously perceived their health as poorer than that of their Comparisons. Indeed, apart from the self-perceived health status, the examining physicians, in their objective observations, recorded no significant group differences as to the appearance of illness or distress and appearance in terms of relative age.

The prevalence of obesity was similar in the Ranch Hand and Comparison cohorts. However, in Ranch Hands, a highly significant positive association between percent body fat and current serum dioxin was found in all of the occupational categories. These results imply a difference in the dioxin pharmacokinetics in obese versus lean participants; but clinically, it is difficult to explain the higher levels of serum dioxin in obese participants relative to any health detriment. It is not clear whether a causal relationship exists between dioxin exposure and increased body fat.

In previous AFHS examinations, sedimentation rate, a sensitive, but nonspecific index of general health usually associated with serious underlying disease, was significantly higher in Ranch Hands than in Comparisons. However, the 1992 examination revealed only a slight clinically insignificant difference in the Ranch Hand enlisted groundcrew and their Comparisons. Analyses showed a statistically significant dose-response effect in the association between sedimentation rate and current serum dioxin in Ranch Hands, but the biological significance is uncertain.

The longitudinal analyses revealed that results from the 1992 examination contrasted with those of previous examinations. Between 1982 and 1987, the percentage of Ranch Hands and Comparisons reporting fair or poor self-perceptions of health was greatly reduced and the difference between the groups had narrowed. However, in the 1992 examination, the change in self-perception of health between 1982 and 1992 was significantly associated with calculated initial serum dioxin levels (of which participants had become aware). The potentially negative effect of known exposure status and serum dioxin level may have affected the more recent results.

In conclusion, the general health of the Ranch Hands and Comparisons appeared comparable by all objective indices; however significant, although possibly biased, group differences were evident in self-perceived health status. Percent body fat and sedimentation rate displayed significant associations with current serum dioxin levels, but the biological significance is uncertain.

Neoplasia Assessment

In the neoplasia assessment, skin and systemic neoplasms were evaluated by behavior, cell type, and location or site. As the anatomic point of contact with industrial toxins and as the only organ system with a clearly defined clinical endpoint (i.e., chloracne) for TCDD exposure, the skin deserves the special emphasis it has received in this study. Although there is no evidence that TCDD exposure causes—or that chloracne is associated with—basal cell carcinomas, the Ranch Hand cohort was found to be at increased risk for the occurrence of these skin cancers in each of the three prior examination cycles.

In the analyses of the 1992 examination, Ranch Hands continued to have a slightly higher prevalence of benign and malignant skin neoplasms than did Comparisons, including basal cell skin cancers at all sites. However, these group differences are no longer statistically significant. Consistent with results from the 1987 examinations, many analyses revealed a significant inverse dose-response with current serum dioxin levels.

Consistent with all previous examinations, none of the analyses revealed any significant group differences in the prevalence of systemic malignancies in the Ranch Hand and Comparison cohorts; neither did the analyses disclose an increased risk of any systemic malignancy in association with either the current or extrapolated initial levels of serum dioxin in Ranch Hands. Longitudinal analyses discovered no significant group differences in the incidence of benign or malignant neoplasms including those thought by some to be related to herbicide exposure (i.e., Hodgkin's disease, non-Hodgkin's lymphoma, and soft tissue sarcoma [STS]).

In summary, at the end of a decade of surveillance, Ranch Hands and Comparisons appear to be at equal risk for the development of all forms of neoplastic disease and there is no evidence to suggest a positive dose-response relationship between body burden of dioxin and neoplastic disease.

Neurological Assessment

The neurological assessment examined historical neurological disorders in addition to central nervous system (CNS), cranial, and peripheral nerve indices, all of which can provide specific clues to the anatomical site of neurological lesions and clarify the need for additional diagnostic studies. The neurological examination is highly sensitive in detecting the presence of peripheral neuropathy, a suspect clinical condition related to TCDD exposure.

The prevalence of historical neurological disorders was similar in the Ranch Hand and Comparison cohorts. In contrast, but of doubtful clinical significance, an inverse dose-response was noted in the analyses relating current serum dioxin to the history of hereditary and degenerative disorders.

In the analyses of the physical examination variables, Ranch Hand enlisted groundcrew, the occupation category with the highest current levels of dioxin, had significantly more cranial nerve index abnormalities than Comparison enlisted groundcrew, but there was no evidence of a dose-response relationship in the serum dioxin analyses. In relation to the extrapolated initial level of serum dioxin, no significant associations were noted for any of the directly measured physical examination variables. The analyses employing current serum dioxin yielded inconsistent results. A positive association was noted in relation to the cranial nerve motor variable smile and the peripheral nerve variables pin prick and patellar reflex, while inverse dose-response patterns were defined for smell and the Babinski reflex.

In summary, the neurological assessment found the prevalence of neurological disease comparable between the Ranch Hand and Comparison groups, and showed no consistent evidence of a dose-response effect with either estimated initial dioxin exposure or current TCDD levels.

Psychological Assessment

Verified psychological conditions and the Symptom Check List-90-Revised (SCL-90-R) inventory of nine primary symptom dimensions and three global indices of distress were examined in the psychological assessment. The SCL-90-R was retained in the 1992 examination because of its effectiveness as a co-measure of variables included in the verified questionnaire as well as to maintain psychometric continuity across the four phases of the AFHS completed to date (Baseline, 1985, 1987, and 1992).

Among the SCL-90-R inventory variables, Ranch Hands exhibited higher psychological distress than Comparisons on the index scores measuring anxiety, obsessive-compulsive behavior, paranoid ideation, somatization, and global severity. A significant group contrast also was exhibited for the verified condition of other neuroses. However, when Ranch Hands were categorized according to serum dioxin levels, significant group differences were revealed only in the contrasts of Ranch Hands with background serum dioxin levels versus Comparisons. The serum dioxin analyses also did not support a dose-response relationship, because there were no significant findings in any of the analyses relating extrapolated initial dioxin and current serum dioxin levels with psychological distress

indicators. Each of the analyses produced a smaller number of significant results from the adjusted analyses than from the unadjusted analyses due to the adjustment for important confounding effects such as education and occupation.

In conclusion, the differences revealed between the Ranch Hand and Comparison cohorts, together with a lack of any effects attributable to dioxin, suggest that factors other than dioxin exposure continue to influence a relatively small but notable number of abnormalities in Ranch Hand test scores. Previous studies in clinical medicine continue to indicate the need for caution when interpreting the outcome of large statistical studies. The possibility that a small subset of physically or psychologically vulnerable Ranch Hands may have suffered psychological injury in the context of their exposure to dioxin cannot be definitively ruled out at this time.

Gastrointestinal Assessment

The historical, physical examination, and laboratory parameters included in the gastrointestinal assessment are well established in clinical practice as screening tools for investigating digestive disorders in outpatients. There are limitations of reliance solely on data from the patient history and physical examination when diagnosing digestive disorders because digestive symptoms are frequently nonspecific and intermittent. However, data collected in the laboratory can provide early insight into the presence of occult liver disease.

Few of the laboratory analyses revealed any significant differences between the Ranch Hand and Comparison cohorts. Ranch Hands had a slightly higher mean alkaline phosphatase than Comparisons, but the difference in the means cannot be considered biologically significant. Analyzed in the discrete form, which is clinically more relevant, the group difference was not significant.

The serum dioxin analyses indicated that estimated initial dioxin exposure was generally not associated with historical liver disorders or current laboratory measurements. However, the analyses revealed that current dioxin levels were often highly associated with lipid-related health indices. In continuous (but not in discrete) form, two of the four liver enzymes studied, ALT and GGT, revealed highly significant positive associations with current serum dioxin levels. Similar results were noted with serum triglycerides and serum cholesterol, which contributed to a negative association between current serum dioxin and the cholesterol-HDL ratio. These results may be explained in part because the analyses of extrapolated initial serum dioxin were adjusted for differential half-life elimination related to percent body fat, whereas no adjustment was made in the analyses of current serum dioxin.

Analyses of the historical and clinical examination variables revealed no evidence of any overt hepatic disease related to the current body burden of dioxin. Most of the statistically significant associations that occurred in relation to the extrapolated initial level of serum dioxin were limited to laboratory indices. These associations more often were found in the continuous, rather than the more clinically relevant discrete, analyses. While the observed dose-response findings are not accompanied by clinical disease, they may still represent subclinical effects.

Over a decade of observation, the longitudinal analyses yielded significant results in several of the laboratory indices. In particular, ALT, serum triglyceride, and cholesterol levels tended to increase over time in Ranch Hands more than in Comparisons. Although these results are consistent with a subtle effect of herbicide exposure on lipid metabolism, the difference was more pronounced in the enlisted flyer category than it was in the more exposed enlisted groundcrew category.

In summary, the gastrointestinal data confirm observations that would be anticipated in a clinical practice and reflect no apparent increase in organ-specific morbidity in Ranch Hands relative to Comparisons nor do they represent an association with serum dioxin levels. Although a subclinical dioxin effect on lipid metabolism cannot be excluded, some of the results may be related in part to body habitus and percent body fat.

Dermatology Assessment

The dermatologic assessment was based on occurrence of acne, location of acne, other dermatologic abnormalities, and a dermatology index based on the presence of comedones, acneiform lesions, acneiform scars, and inclusion cysts, depigmentation, and hyperpigmentation.

In the study of biological effects of herbicides in humans, the dermatologic examination assumes special importance. Of the organ systems analyzed in this report, only the skin has a clinical endpoint (chloracne) that has been related conclusively to dioxin exposure. Experimental dose-response studies in animals and humans have confirmed that the topical concentrations of dioxin required to produce overt lesions are far greater than the concentrations to which participants in the current study were likely to have been exposed during their times of duty in SEA. It is therefore not surprising that, in the four examination cycles to date, no cases of chloracne have been detected.

In general, the dermatology variables showed no significant differences between Ranch Hands and Comparisons. Although the lifetime occurrence of acne, as self-reported by the questionnaire, was similar in both groups, Ranch Hand enlisted groundcrew, those most heavily exposed to dioxin, appeared to be at increased risk for the development of acne subsequent to time of duty in SEA. There is a possibility of bias associated with self-reporting, however, because no group differences were found in the physical examination indices.

In the analyses of extrapolated initial and current serum dioxin, Ranch Hands with current serum dioxin levels above the background level demonstrated lower occurrence of an abnormal dermatology index than did Comparisons. The dermatology index also exhibited a significant negative association with current serum dioxin in Ranch Hands. Although nonsignificant, all other dermatologic indices displayed negative associations with current dioxin. These results provide evidence against a dose-response effect.

In summary, there is no consistent evidence to suggest an adverse dioxin effect on the dermatologic system at levels received by the Ranch Hand cohort in SEA.

Cardiovascular Assessment

The cardiovascular assessment examined historical, physical examination, and questionnaire indices, divided into central and peripheral cardiovascular functions used to alert clinicians to the presence of underlying cardiovascular disease.

The verified historical indices (history of heart disease, hypertension, and myocardial infarction) were similar in Ranch Hands and Comparisons, but the analyses employing serum dioxin measurements revealed inconsistent results. In Ranch Hands, an increase in current dioxin levels was associated with a decrease in the prevalence of verified heart disease and an increase in the history of essential hypertension. Although a plausible biologic explanation for this phenomena is lacking, these results are consistent with findings from the 1987 examination.

In general, the analyses of the central cardiac function variables were not positively associated with serum dioxin. Although Ranch Hand enlisted flyers displayed a significantly higher prevalence of bradycardia than did Comparison enlisted flyers, bradycardia exhibited a significant inverse dose-response with initial and current dioxin. Several other electrocardiograph (ECG) indices, including right bundle branch block (RBBB), non-specific ST- and T-wave changes, and arrhythmias, displayed significant positive associations with current serum dioxin levels, but none of these endpoints also displayed a group difference between Ranch Hands and Comparisons to confirm the dose-response relationship.

The analyses of the peripheral vascular function variables displayed significant group differences for a few of the pulse endpoints among enlisted groundcrew personnel (the occupational category with the highest exposure) and between Ranch Hands with the highest current level of serum dioxin and their Comparisons. However, none of these relationships were reinforced by a significant association with initial or current serum dioxin. In the longitudinal analyses of the pulses endpoints, Ranch Hands were slightly more likely than Comparisons to develop peripheral pulse deficits over time. Again, the analyses using extrapolated initial serum dioxin levels as a measure of exposure did not show consistent evidence of a dose-response relationship.

Dorsalis pedis pulse abnormalities were far more prevalent in both Ranch Hands and Comparisons in the 1985 examination than they were in the 1992 examination. The change in results between the two examinations may relate to the use of different and more accurate Doppler instrumentation in the 1992 examinations. During the 10 years of observation, both Ranch Hands and Comparisons have demonstrated a similar reduction in systolic blood pressure and incidence of hypertension. This trend may reflect the beneficial effects of risk factor identification and life-style modification consequent to participation in this study.

In summary, consistent with the results of prior examinations, Ranch Hands were found to be at slightly greater risk than Comparisons to develop selected peripheral pulse deficits, suggesting some effects from dioxin. These findings are based on the 1992 analysis of hypertension and ST- and T-wave changes, taken in conjunction with the 1994 AFHS mortality update showing an increased number of deaths caused by diseases of the circulatory system among Ranch Hand nonflying enlisted personnel. By all other objective and

subjective indices, the development of cardiovascular disease does not appear to be associated with dioxin exposure or current serum dioxin levels.

Hematologic Assessment

The 13 laboratory endpoints analyzed in the hematology assessment provided a comprehensive evaluation of the three peripheral blood lines (erythrocytes, leukocytes, and platelets). These variables are relied upon heavily to reflect disease of the hematopoietic system and also to alert the clinician to the presence of disease in other organ systems.

Of the laboratory variables examined, only platelet count exhibited significant associations with the dioxin exposure indices. Ranch Hands in the enlisted flyer and enlisted groundcrew categories possessed statistically significant higher mean platelet counts than Comparisons, although the differences cannot be considered clinically significant. Ranch Hands with high extrapolated initial dioxin levels also had significantly greater mean platelet count measurements than Comparisons. These results are consistent with those from the 1987 examination, but the biological significance is uncertain.

In the 1987 examination, the mean white blood cell (WBC) counts, platelet counts, and erythrocyte sedimentation rates (ESR) were each higher in Ranch Hands than in Comparisons, raising the possibility of a subclinical inflammatory response associated with prior dioxin exposure. In the current study, no group differences were noted in either the WBC or, as reported in the General Health Assessment (Chapter 9), the ESR. Furthermore, in the current study, current serum dioxin was inversely related to the prevalence of abnormally elevated WBC counts.

In the longitudinal analyses, a gradual reduction was documented in the total platelet count in each group and across all occupations. Ranch Hands continue to have a greater reduction in the total platelet count over time than do Comparisons, but the means from the current examination are nearly equal.

In summary, there is no evidence from the current study to suggest an association between hematopoietic toxicity and prior dioxin exposure. Based on the analyses of WBC, ESR, and total platelet count, there is no longer any evidence that a subclinical inflammatory reaction may be present in Ranch Hands as was thought possible in the 1987 examination.

Renal Assessment

The renal assessment was based on the medical history of kidney disease, physical examination for kidney stones, and five laboratory indices. Pertinent to the interpretation of these analyses is the frequent finding in ambulatory medicine of isolated abnormalities in the routine urinalysis of healthy individuals who, in fact, have no disease of the genitourinary system. No significant group difference or association with serum dioxin was noted in the history of urinary tract disease, as measured by a verified history of kidney disease and the presence of renal calculi detected by plain films of the abdomen.

Although the prevalence of microhematuria (urinary red blood cell counts) was similar in both groups, Ranch Hands with the highest levels of extrapolated initial serum dioxin had a significantly higher prevalence of microhematuria than did Comparisons. These results are similar to those from the 1987 examination. Although not statistically significant, the analyses employing current serum dioxin yielded results consistent with a dose-response effect; however, the longitudinal analyses indicated that the prevalence of microhematuria has decreased in the Ranch Hand cohort since 1985. Clinically, the finding of hematuria can signal the presence of "silent" renal calculi or neoplastic disease; however, the analyses of kidney stones do not support the presence of silent renal calculi.

In the analysis of urinary WBC counts (pyuria), the enlisted groundcrew Ranch Hands—those most highly exposed to dioxin—had twice the prevalence of pyuria than did Comparisons. Longitudinal analyses also showed that the enlisted groundcrew Ranch Hands are twice as likely as the enlisted groundcrew Comparisons to develop pyuria over time, but the similar prevalence of pyuria in Ranch Hands with low and high levels of serum dioxin does not support a dose-response effect.

The analysis of urine specific gravity documented a statistically significant positive association with current serum dioxin, but the magnitude of the association was not clinically significant. Analyses of serum creatinine and proteinuria revealed no differences between the cohorts.

In summary, the renal assessment displayed no consistent evidence for any detriment, with the possible exception of hematuria, related to current body burden of dioxin or to the estimated severity of prior exposure.

Endocrine Assessment

In the endocrine assessment, analyses were performed on 36 historical medical records, physical examination, and laboratory variables—five of which were analyzed separately for diabetics, nondiabetics, and all participants. These indices provide a comprehensive assessment of thyroid, gonadal, and endocrine pancreatic function in the population under study.

Analyses of thyroid functions did not reveal significant differences between the Ranch Hand and Comparison cohorts. Similarly, the prevalence of diabetes mellitus in the two groups was not significantly different, although significant positive associations were found between current serum dioxin levels and the onset of diabetes, specifically in the early stages requiring only dietary intervention or oral hypoglycemic therapy.

In assessing glucose metabolism, along with examining the possibility that dioxin may be a risk factor for the development of diabetes, significant results were limited to the current serum dioxin analyses. Diabetic Ranch Hands with high levels of current serum dioxin had significantly higher fasting glucose levels than those with lower levels of dioxin. Nondiabetics, on the other hand, exhibited an inverse association between fasting glucose and current serum dioxin and a positive association between 2-hour postprandial glucose and current serum dioxin. Although not statistically significant, serum insulin levels in diabetics,

in contrast to nondiabetics, were inversely related to dioxin levels, indicating that serum insulin decreases as dioxin levels increase in diabetics. These results are consistent with a fundamental impairment of islet cell responsiveness to hyperglycemia with compromised insulin production and point to a potential mechanism for an effect of dioxin on glucose metabolism. However, the analyses of serum C peptide and serum proinsulin yielded no significant results and did not reveal the biochemical mechanisms by which dioxin might have an effect on insulin production and glucose metabolism.

Analyses of gonadal function detected a significant inverse dose-response relationship between current serum dioxin and total serum testosterone in Ranch Hands. These results are consistent with those from the 1987 examination, but the clinical significance is uncertain.

The longitudinal analyses yielded results that would be anticipated over time with no significant differences between Ranch Hands and Comparisons. Age-related increases were documented in fasting glucose, 2-hour postprandial glucose, and the incidence of diabetes, while serum testosterone decreased with age.

In summary, after 10 years of observation, the prevalence of endocrine disease remains similar in Ranch Hands and Comparisons. Although cause and effect remain to be established, the current endocrine assessment provides further evidence for an association between glucose intolerance and dioxin exposure. The possibility is raised that, in a subset of individuals predisposed to diabetes, dioxin may impair insulin production.

Immunologic Assessment

Immunologic competence was assessed by analyzing physical examination and laboratory data from skin tests for delayed hypersensitivity response, cell surface marker studies on a randomized subset of the study population, immunoglobulin quantitation, and autoantibody detection. This evaluation went far beyond typical medical examinations employed for general health assessments, and included elements of measurement used frequently to define specific diseases.

Overall, the immunologic assessment did not reveal any relationships that could be considered clinically significant between dioxin exposure and physiologic abnormalities. The MSK smooth muscle antibody, rheumatoid factor, and lupus panel summary index displayed inverse associations with dioxin exposure, but did not support a dose-response relationship; additionally, the magnitude of these associations was small and could not be interpreted as conveying a health risk.

A marginally significant positive association was found between serum IgA concentrations and extrapolated initial dioxin levels. Although the magnitude of this effect was small, its statistical significance coupled with continuity over time suggests a possible relationship that should be evaluated further because elevated IgA may indicate liver disease, chronic inflammation, or selective immune dysfunction.

The longitudinal analyses of the CD4-CD8 ratio did not consistently show significant differences between the 1985 and 1992 measurements in relation to dioxin exposure.

In summary, these findings do not provide evidence of a clinically significant dose-response effect for body burden of dioxin on parameters of immunologic assessment. The minor, statistically significant relationships that do have a small magnitude bear potential for long-term evaluation to identify trends, but currently cannot be interpreted to indicate specific health impairment caused by immune system dysfunction.

Pulmonary Assessment

The pulmonary assessment consisted of three historical variables, physical examination of thorax and lung abnormalities, and six laboratory measurements. Because the lung is often involved secondarily in numerous infectious, inflammatory, and neoplastic disorders, the assessment of lung disease includes a comprehensive multisystem review conducted during the examinations and reported in other chapters. All episodes of pulmonary disease were verified by medical records review.

In the group analyses, Ranch Hands had a significantly higher prevalence of bronchitis and thorax and lung abnormalities. Conversely, pneumonia was less common in Ranch Hands than in Comparisons, though not statistically significant. Of interest, but of uncertain cause, Ranch Hand enlisted flyers appeared to be more at risk than Comparisons, respecting history of bronchitis and thorax and lung abnormalities; however, there was no evidence from the analyses of extrapolated initial and current serum dioxin measurements to confirm a dose-response relationship.

For the laboratory variables, a statistically significant inverse relationship was revealed between percent of predicted forced vital capacity (FVC) and initial and current serum dioxin in Ranch Hands. However, when Ranch Hands were contrasted with Comparisons, no significant differences were detected. The ratio of observed forced expiratory volume in 1 second (FEV_1) to observed FVC in Ranch Hands also revealed a significant relationship with initial dioxin, indicating that the ratio increased (became closer to 1) for increasing levels of extrapolated initial dioxin; this effect may be due to the diminishing magnitude of FVC in the denominator of the ratio. Although consistent with a dose-response effect, the changes in the ratio were slight and of doubtful physiologic significance.

In the longitudinal analysis of the ratio of observed FEV_1 to observed FVC, a significant group difference was shown for the enlisted flyers. The Ranch Hand enlisted flyers had a larger decrease in the ratio between 1982 and 1992 than did the Comparison enlisted flyers, but the difference is not physiologically significant, and there was no evidence for any trend in relation to the extrapolated initial or current serum dioxin levels.

In summary, the historical, physical examination, and laboratory data analyzed for the pulmonary assessment revealed no consistent evidence of an increased prevalence of pulmonary disease in the Ranch Hand cohort relative to the Comparison cohort or in relation to body burden of dioxin.

INTERPRETIVE CONSIDERATIONS

There are certain facts that need to be understood in drawing conclusions from the statistical analysis of the 1992 followup examination results. For example, there are often difficulties associated with multiple testing. With multiple models applied against hundreds of variables, the likelihood of a statistical test indicating some artifactual association is high. But longitudinal comparisons of previous examinations may show a consistent association, supporting a non-artifactual relationship. However, longitudinal tests of the same population are clearly not independent tests. If a chance association was present at the first physical examination, it would tend to persist in subsequent examinations.

Conversely, depending on putative site and mode of action, the association would be expected to increase with time (if latency or other chronic effects predominate) or decrease with time (if current dioxin level predominates in the mechanism). It is also important to note that some conditions do not appear with reasonable frequency until middle age or later, and, in the early years of the study, an eventual significant increase in relative risk in a population easily might be masked by data too sparse for meaningful analysis.

The putative site and mode of action in the body could itself either cause or obscure a relationship. Receptors might be activated only after a certain dioxin threshold value had been exceeded—that is, a value exceeding the body's capability to safely store dioxin. If, on the other hand, dioxin caused a competitive inhibition of receptor actions normally stimulated by other substances, there might be a "no-threshold" effect. Depending on the nature (lipid or non-lipid) and type of function of the hypothetical receptor site, an increase in body fat over time might either cause an increase in dioxin effect because of a greater volume of distribution or a decrease in dioxin effect because of a lesser concentration at the receptor site.

Strength of association is also an issue in a study of a population this size. A study with a population of 2,233 lacks power to determine increases in relative risks for rare events, because rare events are unlikely to occur in a group this small. While certain occupational toxins have truly pathognomonic pathology (e.g., mesothelioma for asbestos, hepatic angiosarcoma for vinyl chloride) virtually non-existent in the absence of the toxin, other toxins merely increase the risk of non-pathognomonic pathology. For example, in the absence of a dioxin-pathognomonic lesion, this study would likely not discern an increase in the relative risk for a rare tumor. By assessing the pathology observed in association with other known environmental risk factors (e.g., tobacco use, alcohol use) it is sometimes possible to provide an upper bound for the magnitude of effect missed. However, this study has inherent limits in detecting modest increases in relative risk for infrequent pathology.

A final difficulty is the presence of a true association that is non-causal. An example might be a condition not caused by dioxin, but resulting in or from an altered biological dioxin half-life. In this case, a correlation might be high in the total absence of causality.

Clearly, there are many issues to be considered in interpreting data for this study. With these issues in mind, certain assessments were made by looking at a number of factors. Among these factors are longitudinal trends, biological plausibility, consistency with animal

toxicology, the presence of a plausible dose-response relationship, and strength of association. But, meeting all of these criteria would not guarantee causality, nor would failing these criteria guarantee the lack of a dioxin effect. It can be argued, however, that the good faith application of these particular filters should be the starting point for generating hypotheses for experimental examination through in vitro and in vivo testing, as well as through further epidemiological analysis of these and other dioxin exposed groups.

SUMMARY

Based on the statistical findings of the 1992 examination, and subject to the qualifications considered above, the principal investigators have drawn the following conclusions.

Glucose Intolerance

The results indicate a statistically and potentially clinically significant association between serum dioxin and glucose intolerance. This association exhibits a dose response relationship, and is present both for non-diabetic individuals (as manifested by elevated insulin levels) and diabetic individuals (as manifested by increased prevalence and severity of diabetes, and decreased age of onset). This association was found with type II diabetes only. This association was also present longitudinally and occurs in other epidemiological studies in addition to the AFHS.

Cardiovascular Mortality

There is a statistically significant increase in cardiovascular mortality in the most heavily exposed subgroup, the enlisted groundcrew. This association persists longitudinally throughout the three examination cycles. Inclusion of this group with lesser exposed Ranch Hand subgroups results in a statistically nonsignificant overall relative risk. Less clinically severe criteria for altered cardiac functions including ECG findings of prior myocardial infarction, non-specific ST- and T-wave changes, and RBBB displayed significant positive associations with dioxin, although these associations did not cause significant group differences between all Ranch Hands and all Comparisons. Peripheral vascular function variables displayed significant subgroup differences for both the enlisted groundcrew and the high current dioxin category in relation to the Comparisons. Both groups had a greater prevalence of new pulse deficits arising since the 1985 followup examination than did their Comparisons.

Serum Lipid Abnormality

There is a highly significant positive statistical association between dioxin and cholesterol, dioxin and triglycerides, and dioxin and the cholesterol-HDL ratio in most models using either current dioxin levels or dioxin levels extrapolated to the end of the tour of duty in SEA. In such models, the correlation between HDL cholesterol and dioxin was highly significant and negative. These lipid findings were consistent with the 1987 findings, but were not consistent with the 1982 examination when serum cholesterol in Ranch Hands was significantly lower than in Comparisons.

Liver Enzymes

Both lipid-adjusted and whole-weight current dioxin showed elevated mean aspartate aminotransferase (AST), ALT, and GGT associations. For ALT and GGT this association was highly significant. This association had not been present in previous examinations. Although these elevations were statistically significant, mean enzyme levels remained well within normal limits and the prevalence of abnormally elevated liver enzymes was not statistically increased. Thus, although this laboratory finding is statistically significant, the AFHS population did not show any clinically adverse outcomes.

Increase in IgA

A marginally significant increase in IgA with increased serum dioxin was found. This paralleled similar findings of increased IgA, first noted in the 1987 followup. Although this elevation was marginally significant, mean IgA levels remained well within normal limits, and the prevalence of significant abnormally elevated IgA was not statistically increased. Thus, although this finding is statistically significant, the AFHS population did not show any clinically adverse outcomes.

Decrease in Serum Testosterone

A statistically significant inverse effect was seen between total serum testosterone and current dioxin in Ranch Hands. This paralleled similar findings first noted in the 1987 followup. Although this decrease was statistically significant, mean serum testosterone levels remained well within normal limits, and the prevalence of abnormally low serum testosterone was not statistically increased. Thus, although this finding is statistically significant, the AFHS population did not show any clinically adverse outcomes.

Decrease in MSK and Lupus Panel Positives

Significant and marginally significant decreases in the prevalence of positive reactions to MSK, lupus, and rheumatoid factor tests in relation to dioxin were seen in the 1992 followup. When present, these tests are indicative of potential autoimmune disorders. Their absence is therefore not normally considered pathologic, but a decreased prevalence could nonetheless indicate some degree of immune suppression. More specific tests of immune suppression were not significantly associated with dioxin.

No Significant Difference in Incidence or Prevalence of Neoplastic Disease

It has been theorized that dioxin can act as either an inducer or promoter of neoplastic disease. A detailed analysis of all forms of neoplastic disease over the course of a decade show no significant group differences in the incidence of benign or malignant neoplasms, including those neoplasms most often associated with herbicide exposure in the Ranch Hand population (e.g., Hodgkin's Disease, non-Hodgkin's lymphoma, soft tissue sarcoma). In the 1992 followup, there was again no significant group differences. The marginally significant differences in site-specific incidence that were found more often favored a decrease in relative risk associated with dioxin exposure rather than an increased risk. As previously

stated, because of its size, this study does lack power to ascertain modest increases in relative risk for uncommon neoplasms. As the population continues to age, the combination of an increase in background rate of neoplastic disease, increased time for latent effects of past exposure, and increased time of total exposure may combine to increase the power of this study to determine neoplastic effects.

In summary, glucose intolerance, serum lipid abnormality, and cardiovascular abnormality and mortality, are areas demonstrating associations that, if causality were established, would represent the most important dioxin-associated health problems seen in the AFHS to date. These three areas appear to have the greatest magnitude of effect in terms of absolute increase in risk, in common areas known to contribute to years of potential life lost and to overall healthcare costs. Clearly, there are biological interrelationships among all three of these variables that will make the task of establishing causality, as well as establishing primary versus secondary causality, challenging. From a public health perspective, these three areas demand the greatest attention.

CHAPTER 22

FUTURE DIRECTIONS

A careful review of the results of the past four physical examinations provides an opportunity to refine and focus the remaining two examinations of the Air Force Health Study. The current and prior examination outcomes have identified several medical tests requiring more intense evaluation and other analyses that can be reduced or eliminated in the 1997 and 2002 studies without sacrificing scientific value.

Immunological testing of skin test reactivity, T-cell type, and T-cell function were important parts of all four examinations, and high-quality data in this area were gathered in the 1985, 1987, and 1992 studies. After exhaustive evaluation, there appear to be some effects that may be dioxin-related. Therefore, many of these measurements will remain in the 1997 study. However, the skin test reactivity measurement is medically redundant with the battery of cell function tests, and thus will be eliminated from the next examination. Additionally, many of the highly nonspecific tests in the protein profile and lupus panel will be eliminated. Many of these tests are poorly understood by clinical pathologists and immunologists and should be removed from consideration.

The Doppler evaluation of the large artery pulses (radial and femoral) also will be eliminated, reducing examination time and stress on the participants. Our data does not indicate any dioxin-mediated effect on these arteries. However, the relationship between dioxin and diabetes makes it imperative that the smaller arteries of the legs and feet remain a key part of the examination.

Because no association was found between testicular abnormality detected during ultrasound and dioxin, the ultrasound evaluation of the testicles will be eliminated.

Additional dioxin assays will be performed on willing Ranch Hands who have participated in our studies of dioxin half-life. A fourth measurement, taken from blood collected in 1997, will further refine our estimate of half-life, allow study of the fit of the first order elimination model, and permit better estimates of the initial dose in Ranch Hands with elevated current dioxin levels.

The 1997 examination will be expanded to include additional measurements of the cellular metabolism of glucose. The possible development of a laboratory measurement of specific enzymes involved in glucose transport into the cell would be an important addition to the current evaluation of diabetes.